Special Acknowledgment

The editor hereby acknowledges the special contributions of Drs Murray Albert Joseph Fries and William B Sherman who as associate editors for the original series contributed greatly to the development of this book

Fundamentals of MODERN ALLERGY

Edited by

Samuel J Prigal, M D

Sponsored by the New York Allergy Society

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FUNDAMENTALS OF MODERN ALLERGY

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DEDICATION

To the memory of

Robert Chobot

Selian Hebald

Bret Ratner

Will C Spain

each of whom contributed much

to the field of allergy

FOREWORD

It is of interest to compare the development of different branches of medicine The signs symptoms and lesions of tuberculosis are so varied that before the discovery of tubercle bacilli and their demonstration in certain lesions it was not recognized that tuberculous meningitis tuberculous caseous pneumonia miliary tuberculosis chronic pulmonary tuberculosis tuberculous osteomyelitis or lupus vulgaris are related to each other Only the *recognition of the agent of infection* in this case the tubercle bacillus made it possible to develop our knowledge of the pathogenesis and the clinical aspects of this disease

Similarly the *manifestations of allergy or allergic diseases differ inordinately* Compare for example asthma angioedema contact dermatitis food allergies drug allergies with hematological disorders stings by insects or various manifestations of serum sickness In tuberculosis a broad spectrum of the disease is connected by the common agent of the infection The disease is the result of the relationship between *the agent of the infection and the host* Our knowledge of the pathogenesis and of the disease of tuberculosis is inseparable from the causative agent *In allergy the inciting factors are extremely varied and so are the manifestations elicited by them*

The science of allergy was initiated with a new concept To explain serum sickness von Pirquet and Schick postulated that the parenteral introduction of an innocuous foreign protein into animals results in an altered specific hypersensitivity to those proteins Many of the essential aspects of allergy such as specificity of the antigenic material anaphylaxis and formation of precipitins soon established the immunologic character of allergy

Landmarks in the development of our knowledge of allergy indicate many directions (skin sensitizing antibodies blocking antibodies purification of allergens sensitization to drugs with reference to blood platelets) There are diseases which are allergic per se but there are other allergic conditions in which an allergic component may be assumed to be a part Periarteritis nodosa lupus erythematosus scleroderma and rheumatoid arthritis may be mentioned Precipitin formation against thyroglobulin in persons with chronic thyroiditis may be the result of autosensitization

Progress in our knowledge of allergy will continue to come from several sources One of these will be immunochemistry which recently benefited greatly by the utilization of the agar double diffusion technique by the use of immunological adjuvants as well as by the purification of allergens and antibodies Many of the questions and answers in allergy are derived from clinical medicine including pediatrics the diseases of organ systems such as the respiratory digestive and genitourinary systems and the skin and eye diseases It is safe to say that the meeting of various specialties and allergy in the future will be even more fruitful than it has been in the past The chemical industry benefited our economy by producing an enormous number of new compounds—many of them now problems for the allergist

In the past prophylaxis depended on avoiding contact and treatment depended on desensitization hyposensitization and pharmacological agents Recently endocrinological material of synthetic and of animal origins have been studied on a fairly wide scale While the results are interesting from the standpoint of immunology biochemistry and endocrinology the clinical allergist thus far has not received satisfying answers to practical questions of therapy

In all branches of medicine and especially in experimental pathology the *same disease symptoms do not necessarily mean that the causative agents are the same* The investigator should always be mindful of the fact that certain organs can react only in one or in a very limited number of ways to a great diversity of stimulants and enzymes In the field of allergy much effort has been spent to demonstrate factors which show that different phenomena are based on the same pathogenesis

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THE NEW YORK ALLERGY SOCIETY

HISTORICAL NOTE

The New York Allergy Society with approximately 250 members practicing in the metropolitan area of New York City is the largest local allergy society in the world. It has been a pioneer in many undertakings and has had an important role in the growth and development of the field of allergy not only locally but indirectly on the national and international scenes.

New York City became at the very outset a leading center for research in allergy owing to the pioneer efforts and interests of Dr. Robert A. Cooke and the men he gathered about him. In 1918 Dr. Cooke established the first allergy clinic in New York City. Such names as Spain, Vander Veer, Brown and Chobot (all deceased now) to mention only a few, were associated with Dr. Cooke in these developments.

As the field of allergy grew and clinics patterned after Dr. Cooke's clinic were organized in various hospitals, it became necessary to establish standards for newly formed allergy clinics. This was achieved by the loosely formed organization called the Association of Approved Allergy Clinics of New York. This association functioned from 1937 to 1947 giving way to the more highly organized New York Allergy Society following the reorganization of its parent society in 1947.

The New York Allergy Society has devoted its attention not only to the improvement of the allergy clinics but to the furthering of the practice and knowledge of allergy in general. This has been achieved through its primary function of holding clinical and scientific sessions in the field of allergy. In the last few years its activities and horizons have been broadened with active participation in the field of education of the general physician in allergy. It was this that prompted Dr. Samuel J. Prigal to initiate the writing of a series of articles by the members on various aspects of allergy. These articles

were published in the *New York State Journal of Medicine* and were subsequently encompassed within this book In this endeavor Dr Prigal was ably assisted by the Editorial Board of the Society With the same purpose in mind a course based on The Fundamentals of Modern Allergy was also given by the membership to a group of general physicians

The New York Allergy Society has taken an active part in the recognition of notable events in the history of allergy In 1956 the Society participated in the semicentennial exercise in honor of the founding of the science of allergy on which occasion Dr Bela Schick was signally honored In 1958 the Society honored Dr Robert A Cooke on the occasion of the fortieth anniversary of his opening of the first allergy clinic in America

Other activities of the Society have included strong and active support of such national organizations as The Academy of Allergy and The American College of Allergists on the occasions of their scientific meetings in New York City The New York Allergy Society has also been an active supporter of The Allergy Foundation since its inception and its members have played leading roles in its development and progress

The Society is very proud of this book which is an expression of the cooperative efforts of its membership This has been an unusual project not previously conceived by any similar organization We hope that this will stimulate further activity in the Society and perhaps in other organizations concerned with the education of physicians interested in the field of allergy

Aaron D Spielman, M D
President 1959–1960

PREFACE

It has long been my belief that there is a need for dissemination of the basic principles of allergy among general practitioners and senior students The New York Allergy Society agreed to participate in a project which resulted in the publication of the series Fundamentals of Modern Allergy in the *New York State Journal of Medicine* and its eventual development into this book The Society the largest local organization of allergists in the world includes in its membership so many men who pioneered in the field and who have contributed to its growth and development that it afforded the editor a unique source for such a compendium

The original series designed to be both practical and informative was well received Originally only 26 subjects were planned but as the series gained momentum it became apparent that more would have to be included the series finally reached a total of 63 subjects Perhaps it may surprise the reader that the allergy covers such a broad territory yet as shown in this book the field is growing ever broader

Only two chapters of the book did not originate in the series as published by the *Journal* These are the chapter Treatment of Emergencies in Allergy by Loveless which is a condensation and modification of her earlier reports in the Medical Emergencies number of the *Medical Clinics of North America* and in the *New York State Journal of Medicine* and the chapter Cardiac and Allergic Asthma by Swineford which originally appeared in *Postgraduate Medicine* Most of the articles in the series were published in the *Journal* under the series title Fundamentals of Modern Allergy Two articles one by Fuchs (The Common Cold and Allergic Rhinitis) and one by Kaufman (Serum Sensitivity Tests and Antitoxin Administration) which originally appeared in the *Journal* as independent articles were ultimately incorporated into the book in order to broaden its scope and usefulness

In the consideration of the subjects to be covered by the original series and later by the book my editorial associates and I bore in mind that many physicians have never had formal instruction in allergy since this is a relatively new discipline in medicine Moreover many aspects of allergy are controversial since this is a highly

dynamic field and is broad in its coverage—there is no part of the anatomy that cannot be involved in the allergic reactions As for the student he is now being exposed to new and broader concepts of allergy yet since there are only a handful of schools with a chair of allergy the teaching of this specialty remains inadequate

The role of infection in inducing allergy whether to the infecting agent itself or to the alteration or modification of the host s protein is only now beginning to be appreciated Therefore infection particularly in relation to asthma receives special consideration Since infection implies some degree of contagion this aspect is also treated

The role of the psyche in allergy likewise needs exploration Many physicians deny or belittle the role of the antigen antibody mechanism and prefer instead the rationalization of symptoms by Freudian concepts Due consideration is therefore given to this controversial subject

Allergy must be considered as a possible cause of the baffling collagen diseases Likewise, the role of allergy in kidney diseases is explored in one chapter

New on the horizon of allergy is the problem of autoantibodies and autosensitivity Ehrlich gave this concept considerable thought and attention and dismissed it as a cause of disease In this book there is an excellent review of the subject since some diseases can now be shown to be caused by this phenomenon and in others autosensitivity may play a supportive role

Although this book is designed primarily for the general practitioner and the student the allergist also will find in it useful and provocative material on topics such as enzyme mechanisms in allergy histamine liberators rehabilitation of the patient with chronic asthma climate and asthma botany of allergy and anesthesia for the allergic patient in addition to those mentioned above These are subjects not considered in standard texts

Those who treat pulmonary diseases in addition to asthma will find of special interest the chapter on asthma in relation to bronchitis emphysema bronchiectasis and other pulmonary diseases Basic in its contribution is the beautifully illustrated chapter on pathology it adds much to the value of the book

The author of each chapter was selected for his special knowledge in the field In most instances there were members of the Society who were so qualified To each of these contributors I am indebted for his labor For some subjects specially qualified nonmembers were selected These include Milton Adelman George Baehr Elmer Becker Milton Bohrod Bernard Halpern Kurt Lange Mary H Loveless Philip R B McMaster Bela Schick and Oscar Swineford Jr These

generous collaborators have done magnificently in filling the breaches so that the book emerged as a fully rounded symposium Special thanks go to each of them for his contribution to this endeavor

Gratitude is expressed to the *New York State Journal of Medicine* for permission to reprint those chapters which originally appeared in the *Journal* To Dr Laurance Redway editor and to Miss Alvina Lewis assistant to the editor of the Journal I am most grateful for their exceptional cooperation Thanks are due also to *Postgraduate Medicine* for permission to reprint Swineford s chapter Cardiac and Allergic Asthma and to the W B Saunders Company for permission to reprint a chart from Cooke s Allergy in Theory and Practice and a table from their Manual of Clinical Allergy by Sheldon Lovell and Mathews

Finally mention must be made and appreciation acknowledged to Mrs Phyllis Barkan my secretary and to my wife Ada who devoted long hours of labor to retyping proofreading and attending to countless number of things attendant on the writing of a book

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PART FIVE GENERAL TREATMENT AND PROPHYLAXIS IN ALLERGY

PART FIVE GENERAL TREATMENT AND PROPHYLAXIS IN ALLERGY

INTRODUCTION

Allergy one of the newest disciplines in medicine i
of explanation to the average physician Many have ha
instruction in this subject since formal instruction in
introduced in medical schools relatively recently Abou
medical schools at present give no formal instruction i
spite the high incidence of allergic diseases in genera
these reasons the New York Allergy Society initiated i
of articles of special interest to the general practitioner
published for over two years in the *New York State J*
cine and serve as the basis of this work

As the title indicates the book considers briefly
of allergy with emphasis on diagnosis and treatm
problems can readily be treated by the family p
that he is adequately prepared and it is hoped tha
useful for such preparation

There are certain aspects of allergy which may
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highly kinetic and reversible phenomenon (althou
ceptions as will be shown in Chapter 1 The Scope
Cooke) Most physicians however have grown accus
of disease in terms of pathology and when they are co
disorders of physiopathology they are puzzled The
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itiated by inherently nontoxic substances Even esser
drugs become toxic and at times lethal (e g penicilli
to these substances has developed This sensitivity
long lasting sometimes evanescent both types of
occur with the same food or drug in different individ
same circumstances without any apparent explanation

gens may produce a variety of reactions penicillin for example may produce urticarial and angioedema type reactions when used for the first time and then may be subsequently tolerated On the other hand some individuals develop asthma or anaphylaxis with repeated use of this antibiotic particularly after the resumption of therapy following a period of no treatment

Allergy has been closely linked to immunity since both are mediated through antigen antibody reactions Unlike immunity which is protective allergy may be not only deleterious but highly destructive No wonder then that Coca a pioneer in allergy coined the word atopy (strange disease) for the condition of those allergic individuals who have a hereditary background of allergy and in whom blood studies or skin testing reveals the presence of skin sensitizing antibodies

To complicate matters further sensitivities may disappear spontaneously or on the other hand may spread to encompass more allergens or may manifest themselves in new forms involving new shock organs

It is also difficult to comprehend the intimate relationship between allergy infection and the psyche Allergy may be modified by either infection or a psychodynamic mechanism singly or in combination At times severe allergy may induce psychologic disorder (somatopsychic reaction) just as the emotions may aggravate latent or mild allergic disease (psychosomatic reaction) There are times when symptoms originating from an allergic mechanism are perpetuated either by infection or by psychodynamic factors long after the allergen has been removed Also little is known of the role of the Pavlovian conditioned reflex in relation to allergy

No attempt is made in this book to answer all the questions confronting the allergist since they are not all answerable even by the expert There are certain misconceptions commonly encountered however which need to be dissipated These include such notions as the following

1 That children outgrow their allergy Some do but most do not and develop complications (sinusitis bronchitis emphysema etc) which could be avoided by proper allergic management and which if untreated may plague them for a lifetime Asthma can be crippling and the doctor should not wait for miracles to happen

2 That skin testing is dangerous and should be avoided particularly in children Although there is an element of danger this should not be a deterrent if skin testing is understood and adequate precautions are taken

3 That no allergic investigation or treatment is indicated if the

patient's symptoms respond to medication This is not true particularly if the medication is cortisone and related drugs Nor does this hold for persistent allergy since it is undesirable for the patient to take medication for a lifetime It is far better to search for the cause and to remove it or to modify the allergy where possible by specific injections In the case of hay fever symptomatic treatment with the antihistamines may relieve the hay fever but may result in something worse and usually preventable by injections—asthma

4 That positive reactions to skin tests indicate specific allergy This is only partly true the reactions must be correlated with the clinical picture

5 That patients with symptoms caused by pollens should not be treated during the pollen season This too is only partly true They should not be given the injections usually given in preseasonal therapy but they can be given effective coseasonal therapy with smaller doses frequently administered (see chapters on hay fever)

It is the hope of the editor that this book will help to dispel these false notions and more positively to initiate procedures of genuine value to the practitioner and his patient

Special emphasis has naturally been placed on the most common allergies—asthma hay fever eczema and urticaria The editor believes however that the practitioner should also be familiar with the less common allergies involving the gastrointestinal hemopoietic and central nervous systems The reader will also be introduced into highly controversial aspects of allergy in the discussions of collagen diseases and the nephritides New on the horizon of allergy or covered for the first time as a full chapter in a text are such subjects as autosensitivity the role of allergy in cancer and transplantation an enzymatic approach to allergy histamine and processes of histamine liberation climate and asthma rehabilitation of the asthmatic patient relationship of asthma to bronchitis emphysema etc allergic reactions to vaccines allergy and geriatrics aerosol therapy the treatment of emergencies in allergy prophylaxis in allergy and a listing of agencies and institutions concerned with allergic diseases

It was only natural that differences in points of view should appear since so many authors participated and since many areas in allergy are still controversial Opportunity was given to each author to express himself as an individual and in his own style In only two instances has the editor expressed disagreement with contributors this disagreement is expressed in editorial footnotes leaving the authors free to express themselves fully in the text

One controversial point that deserves comment at this time is the role of surgery in the treatment of infections of the tonsils adenoids

and paranasal sinuses in patients with asthma The question still remains unsettled and in this book several points of view are expressed This problem may be resolved in the future in view of the increased use of antibiotics In the meantime it may be advisable not to adopt a rigid attitude for or against surgery Surely the happy medium will prevail and in time the indications for surgery will become more clearly defined

Baehr s discussion on collagen diseases also merits comment since he gives scant credence to an allergic mechanism for these puzzling ailments except for periarteritis nodosa and possibly lupus erythematosus Bohrod in Chapter 10 supports the allergic concept in the collagen diseases as does McMaster in Chapter 6 Recently the demonstration of antinuclear antibodies in systemic lupus erythematosus has heightened the search for more evidence of hypersensitivity in this and other collagen diseases Perhaps we can summarize these opposing contentions by indicating that although there is presumptive evidence of an allergic cause for the collagen diseases (differing from the common atopic allergies) the case has not been completely proved

Samuel J Prigal

Robert A Cooke | 1

THE SCOPE OF ALLERGY

It is impossible even in this day to define allergy in a way that is completely satisfactory or generally acceptable and the reason is the existing ignorance of many basic phenomena To be sure there is a certain group of diseases which are admittedly allergic such as seasonal and perennial rhinitis some of the types of asthma certain dermatoses spoken of as intrinsic dermatitis (eczema) and those of extrinsic origin the various forms of contact dermatitis and some of the urticaria angioedema group The reason for acceptance of these diseases as allergic is the fact that in many but not all of them there is a demonstrable mechanism the so-called *skin sensitizing* antibody The presence of this antibody is demonstrated by the fact that when the specific allergen is introduced into the skin as a test it gives rise to the immediate wheal reaction The antibody also circulates in the blood plasma of the sensitized (allergic) individual whose serum or plasma injected into a normal nonsensitized person conveys the same sensitization for varying but relatively short periods of time This test is known as the Prausnitz Kustner phenomenon of passive transfer

The type of allergy thus conveyed is spoken of as the immediate edema wheal reaction because of the promptness (five to fifteen minutes) with which the reaction begins when the sensitized person comes in contact with the proper antigen Diseases such as those mentioned above due to this kind of sensitization are accepted as allergic in origin because of the known mechanism and the nature of the resulting lesion In addition to the immediate edema reaction

this group is characterized by certain other features There is an antecedent history of allergy of one sort or another in a large per centage of cases *the patients themselves are apt to have or to have* had other forms of allergy they are frequently sensitive to several or many different substances known as allergens These sensitiza tions develop as we say spontaneously that is there has been no unusual or purposeful contact by artificial measures and although there may have been some natural contact it is only of a degree to which mankind is normally exposed without becoming sensitized

Another feature is that the allergies as a rule are *long lasting ex tending even throughout an entire life span* One might refer to them as apparently self perpetuating and very different from an in duced sensitization such as serum disease following the injection of antiserum The lesions for the most part edematous are reversible and once the reaction is past the tissues return to an essentially nor mal state A tissue or blood eosinophilia is a common accompani ment

Enough now for the immediate reactions Let us discuss a second group of allergies in which the reaction is delayed for it is largely due to their recognition that the scope of allergy has been broad ened The tuberculin test response which when positive appears in twelve to twenty four hours is the prototype of these delayed reac tions One important point is that it is highly specific For years the *allergic nature of a positive Mantoux reaction* was *postulated* largely on the basis of its specificity but a technic akin to the Prausnitz Kustner passive transfer was needed to establish proof that the reaction was due to something in the nature of a sensitizing anti body which could be passed from a sensitive to a nonsensitive indi vidual This method was forthcoming a few years ago when Chase transferred a specific delayed tuberculin reaction from a tuberculin *positive animal to a normal one by means of the lymphoid cells of a* peritoneal exudate and spleen but not by serum

Now we are in a position to go back and describe a little more ac curately what we mean to convey by the word allergy and the al lergic state The tissue reaction and lesions responsible for the symptoms are based on the antibody mechanism which in turn is the basis of sensitization As a result of this the sensitized cell in contact with antigen reacts in a way that the normal cell cannot and this happens irrespective of whether the antibody is responsible for an immediate or a delayed reaction This is what distinguishes an allergic reaction from toxic or pharmacologic responses for these latter are common to all members of a species and do not require the conditioning of the cells by antibody

As was intimated above, it is essentially in the realm of these delayed reactions and largely due to our recognition of them that the field of allergy has been broadened and the horizon extended. Let us discuss this a little further.

There are still many diseases of unknown origin, and some of them are being explored for their basic mechanism, because the search for mechanisms responsible for cellular changes of disease is today the dominating, the impelling factor in medical research, not the study of the lesions themselves.

It is natural, then, that investigation should turn to the hypothesis that sensitization may be the key to the lesions of certain diseases, if not as the total explanation, at least as a factor in certain phases of the pathology. This is exactly what has taken place in regard to the caseating and granulomatous lesions in tuberculosis, for example. No one would pretend to claim that tuberculosis is an allergic disease per se, but it is a progressive step to appreciate that certain of the lesions have an allergic component apart from the toxic factors of the infection.

If one reads the more recent literature dealing with histopathology from most reliable and authoritative sources, one cannot help but be impressed with the types of lesions and diseases that are being discussed and explored from the point of view of allergy as an element in the total picture (see Chap. 10). There are several methods that may be used in such studies. One is through the production of lesions as a result of immunologic procedures.

For example, as a result of the injection of massive doses of a foreign serum in rabbits, Rich produced lesions after an incubation period which closely resembled those found in periarteritis of man.

It is also possible by some special technics to make an animal sensitive even to its own tissues by the production of what are known as autoantibodies or isoantibodies. These are specific for the tissue used to stimulate the antibody. In this way an animal may be sensitized to its own organs, e.g., brain, nerve, or kidney. These studies of lesions and symptoms experimentally produced have as their aim the understanding of such diseases as multiple sclerosis, glomerulonephritis, and others (see Chaps. 6 and 38).

In other words, it is the similarity of pathologies and symptomatologies induced in animals to those of various diseases of man that forms the basis for a concept of allergy as a factor, because the experimental animal, by the immunologic procedures used, has developed on occasion one evidence of a sensitization to the injected antigens—precipitins.

In order to give a general idea of the scope of allergy, let me state

that practically every organ and tissue of the body may respond with a reaction if its cells are sensitized that is contain antibody if or when contact with the antigen is established The substances to which sensitization may exist comprise almost every absorbable material that reaches the body cells through inhalation ingestion infection injection and external contact Thus all inhaled air borne dusts such as pollens danders and molds all ingested foods and drugs the products of bacterial and viral infections the injected drugs and biologicals as well as the many and various substances externally contacted such as cosmetics fabrics and dyes are included In addition and to be more specific an allergy may be shown to be an important contributing factor in those infectious diseases which give a specific delayed reaction such as tuberculosis syphilis typhoid fever brucellosis tularemia glanders lymphogranuloma and the dermatophytoses

Among diseases in which allergy is reasonably considered a component although not evidenced by an immediate wheal reaction we may mention as examples rheumatic fever rhematoid arthritis periarteritis glomerulonephritis urticaria and angioedema the purpura group including thrombocytopenia agranulocytosis and the erythema group

In addition we may properly include many diseases of the eye such as scleritis and episcleritis iritis and uveitis and conjunctivitis and also diseases of brain spinal cord and peripheral nerves Less likely to reveal an allergic component but still under study are acute lupus erythematosus thromboangiitis obliterans scleroderma dermatomyositis and nephrosclerosis

This is truly a formidable list but it reflects the breadth of present day thinking and probing for explanations in many diseases and lesions of disease of unknown or uncertain pathogenesis It is important even though to some extent it is still in the realm of hypothesis It also indicates the importance of a knowledge of the principles of allergy and of a familiarity with the many common allergic diseases themselves on account of the frequency with which they are encountered in general practice

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2 | *William B Sherman*

TYPES OF ALLERGIC REACTIONS

Allergy may produce many different types of pathologic lesions affecting many different organs of the body [1,2] The most familiar type is the immediate reversible reaction in which local edema vasodilation spasm of smooth muscle and activation of mucous glands may occur within a few minutes after contact with the specific allergen In most cases these lesions last a few hours and subside without leaving any residual changes Common examples are hay fever bronchial asthma and acute urticaria The violent and sometimes fatal anaphylactic reactions to penicillin heterologous serum and bee stings are of the same type Patients who survive the acute emergency usually recover completely in a few hours In a large proportion of allergies of this type skin tests with the specific antigen produce an urticarial reaction which also is immediate and completely reversible

Other allergic lesions consisting of exudation infiltration of wandering cells and proliferation of histocytes develop more gradually and last for days or weeks but subside with slight or no scarring Examples of these more gradual reactions are erythema nodosum purpura Loffler s syndrome and the arterial lesions of serum sickness and drug allergy

Finally there are other allergic lesions in which necrosis of tissue is a striking feature for example the lesions of tuberculin allergy and the Arthus phenomenon These lesions develop slowly and heal gradually with the formation of scar tissue They are usually classed as delayed reactions although microscopic studies of the Arthus

lesion show that the initial changes in the small blood vessels are immediate occurring within a few minutes after the injection of antigen

These varied pathologic changes do not necessarily reflect different types of immunologic mechanisms In a rabbit experimentally sensitized to horse serum all three types of lesions—acute anaphylactic shock vascular lesions simulating those of rheumatic fever and periarteritis nodosa and the Arthus reaction—may be produced at will by injecting the same antigen under varying conditions of time dose and route of injection

Those allergic reactions in which the immunologic mechanism is clearly demonstrable are most satisfactorily classified according to the type of sensitization involved These fall into two main categories one in which antibodies are generally present and detectable in the circulating plasma and another in which no circulating antibodies can be detected The first group includes all the immediate allergic reactions—anaphylaxis and the atopic diseases of the asthma and hay fever group In the anaphylactic group may be included serum sickness and the Arthus reaction which are not clinically immediate reactions but which depend on the same type of sensitization as anaphylactic shock

This category of immediate reactions is divided into the anaphylactic sensitizations which are usually artificially induced and the atopic diseases hay fever asthma and urticaria which develop spontaneously Anaphylactic sensitization is readily induced in essentially all individuals of a susceptible species by artificial injections of antigen but develops spontaneously only after unusual exposures to antigen such as bee stings Atopic diseases develop in certain individuals apparently predisposed by heredity after normal casual contacts by inhalation or ingestion with antigens which do not affect the majority of individuals so exposed They are not readily induced artificially by injections of antigens even in persons who have previously manifested their susceptibility by spontaneously developing allergy to other antigens

The types of circulating antibodies differ in the anaphylactic and spontaneous (atopic) sensitizations In the anaphylactic type the circulating antibodies usually show the precipitin reaction and induce passive anaphylaxis in the guinea pig Often they also show the property of passively sensitizing normal human skin to produce the Prausnitz Kustner reaction The plasma or serum of patients with asthma or hay fever on the other hand does not precipitate antigen or passively sensitize guinea pigs The demonstrable evidence of the presence of circulating antibody is the property of inducing the

Prausnitz Kustner phenomenon of passive sensitization of normal human skin

In the delayed type of allergic reactions such as contact dermatitis and delayed bacterial allergy (of which the tuberculin reaction is the classic example) the plasma does not manifest evidence of antibodies by any of the phenomena mentioned above However in experimental animals sensitization of these types can be transferred to normal animals by injecting suspensions of lymphoid cells from the lymph nodes or spleen Bacterial sensitization can be similarly transferred in human beings by suspensions of leukocytes but attempts to transfer contact dermatitis in humans have usually failed The phenomenon of passive sensitization by transfer of cells is believed to indicate the presence of some form of antibody fixed in the cells but absent from the plasma

The sensitizations of the delayed group are readily subdivided according to the method of development of the allergic state Contact sensitization is most readily induced by application of the allergen to the surface of the skin injection deep into the tissues rarely elicits sensitization Bacterial allergy of the tuberculin type develops naturally as a result of the presence of living bacteria in the tissues It is not induced by injecting the antigen (tuberculin) unless it is combined with adjuvants which produce an inflammatory reaction at the site of injection

The type of sensitization which develops in response to an antigenic stimulus depends on the chemical nature of the antigen the route by which exposure takes place the dose of antigen and the hereditary background of the individual The substances producing anaphylactic or atopic sensitizations are usually typical protein antigens while those producing contact dermatitis are more often chemicals of low molecular weight which combine with tissue proteins as haptens The importance of route of contact with the antigen is apparent in hay fever where inhalation of pollen antigen produces sensitization but injection of the same antigen under the skin does not

The differing antibody mechanisms of the immediate and delayed types of allergy give rise to very different physiologic and pathologic changes on subsequent exposure to the antigen In general the delayed types of sensitization cause direct injury or necrosis of cells which come in contact with the antigen with little regard to the tissue structure or function Thus cells from tuberculin sensitive animals grown in tissue cultures undergo necrosis when tuberculin is added to the culture medium Little is known of the mechanism of this reaction it is not affected by antihistamine drugs

The immediate allergic reactions, on the other hand, take place chiefly in certain *shock organs*, where the antibodies are apparently present in higher concentrations than elsewhere in the body. The tissues most generally involved in immediate allergic reactions are smooth muscle, the small blood vessels, and the mucus-secreting glands. Characteristic reactions are spasm of smooth muscle of the bronchial and gastrointestinal systems, erythema due to dilatation of small vessels, edema due to transudation through the walls of vessels, and increased mucous secretions.[4] Table 1 summarizes the characteristics differentiating the immediate and delayed type reactions.

TABLE 1 TYPES OF ALLERGIC INFLAMMATORY RESPONSES

	Early responses		Delayed responses
	Wheal and erythema	Arthus or anaphylactic	
Clinical state	Hay fever, asthma	Serum sickness	Tuberculosis, lymphogranuloma, histoplasmosis, syphilis, poison ivy
Sensitizing material	Pollens	Soluble proteins, carbohydrates	Bacteria, viruses, fungi, spirochetes, plant materials, simple chemicals
Antibody	Present in serum Nonprecipitable Heat labile	Present in serum Precipitable Heat stable	Absent in serum Unknown
Transfer of sensitivity	With serum	With serum	Not with serum With cells
Cytotoxicity of antigen for explanted sensitive cells	None	None	Present

SOURCE After Lawrence, Am J Med 20 478 (1956)

Some of these reactions, particularly those of smooth muscle spasm, can be demonstrated in tissue excised from the body and kept alive in perfusion fluids. In the Schultz-Dale reaction, strips of smooth muscle from the uterus or intestine of an anaphylactically sensitized guinea pig are shown to contract vigorously when the specific antigen is added to the perfusion fluid. Schild *et al.*[3] demonstrated a similar reaction of smooth muscle from the bronchioles of a patient with asthma due to grass pollen who underwent a lobectomy for bronchiectasis. When grass pollen antigen was added

there was a prompt contraction These reactions like the reaction of tuberculin sensitive cells in tissue culture show that allergic re actions can take place independently of the central nervous system

Many of the physiologic reactions which take place in the im mediate types of allergy resemble the actions of histamine and are inhibited to a considerable degree by adequate concentrations of antihistamine drugs In many such reactions the actual release of histamine may be demonstrated when excised tissue is exposed to the ant gen Thus the blood cells of a patient with ragweed hay fever release histamine when ragweed antigen is added to the blood in a test tube There is no doubt that histamine released as a result of the antigen antibody reaction plays an important part in the production of the physiologic changes observed in the immediate allergic reactions In the anaphylactic reactions of certain species of animals other intermediary compounds such as acetylcholine serotonin heparin and an unknown substance denoted only as slow reacting substance are also important in some instances more so than histamine

The relative importance of these other intermediary substances in human allergy has not been clearly demonstrated but there is evidence that they may play some part In patients susceptible to asthma attacks may be elicited by small doses of either histamine or acetylcholine (Mecholyl) Serotonin from intestinal carcinoids in patients can cause asthmatic symptoms without specific sensitization but does not cause spasm of bronchial muscle on direct contact [5]

Persons anaphylactically sensitized to horse serum by previous injections of antitoxin have different antibodies (precipitins and antibodies which passively sensitize guinea pigs) from atopic per sons spontaneously sensitive to horse protein Yet the shock reaction produced by an injection of antitoxin prepared from horses is simi lar in both presumably because the same intermediary products notably histamine are released by both antibody mechanisms

None of the intermediary agents which take part in the immediate type of allergic reaction are known to be involved in the produc tion of delayed allergic reactions The lesions of contact dermatitis contain more histamine than normal skin but it is apparently bound in such combinations that it does not produce its usual physiologic effects None of the delayed allergic reactions are effected by anti histamine drugs

In each type of sensitization the reaction produced by the specific antigen depends largely on the dose and the route of exposure which determine the distribution of antigen in the body In hay fever the usual shock organ is the nasal mucosa since this is the portion of the

body naturally exposed to the antigen However the sensitization is general rather than local Intracutaneous injections of antigen produce a wheal and erythema reaction in skin tests If too large an amount of antigen is injected either in the skin test or in treatment it spreads through the circulation and elicits reactions in various other shock organs manifested by asthma uterine cramps and occasionally vasomotor collapse

Tuberculin sensitization is also generalized but there are no special shock organs The local reaction to the injection of antigen can be elicited in essentially any tissue of the body including the cornea which does not take part in immediate allergic reactions because of the absence of blood vessels When a systemic reaction is caused by injection of too large a dose of tuberculin it is characterized by fever and general malaise without involvement of any particular shock organ There may be focal inflammatory reactions at sites of tuberculous infection This localization is probably due to the fact that cells in these areas are already exposed to tuberculin

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ALLERGENS

ALLERGENS IN GENERAL

At present there are no *specific* chemical or physical criteria which can be used to predict whether or not a substance will be antigenic One may have to consider not only the substance but also the ability of the organism to produce antibody which in turn may be influenced by hereditary factors However several generalizations may be made Large molecular weight is associated with antigenicity Proteins have large molecular weights because they are formed from polypeptide chains which are coiled up and looped back upon each other being held together by hydrogen bonds formed through the hydroxyl groups of the hydroxy amino acids The shape of the large protein molecules is determined by the way that the polypeptide chains are bound together and this in turn is determined by the concentration and variety of amino acids present Proteins may be oval rod disk or sphere shaped Immunologic multivalence depends upon the number of similar molecular groups which emerge upon the surface of the molecule N times In other words when there is more than one of the same kind of grouping a multivalent substance is present

Heidelberger and Avery[1] demonstrated the important role that polysaccharides play as antigens when they isolated a soluble specific substance from the Type II and III pneumococcus and showed it to be a pure carbohydrate The possibility of innumerable polysaccharide antigens is just as understandable as the diversity of protein antigens A large number of immunologically specific polysac

charides arise from the asymmetry of the carbon atoms in the sugars and sugar acids the alpha and beta glucoside unions and different modes of unions of the various sugars

Undisputed proof of the antigenicity of lipids has not occurred Generally there is a trace of protein present in the phospholipid or sterol which accounts for the antigenicity

PROTEINS

Kammann [3] in 1901 found that the activity of rye pollen resided in the protein fraction as shown by tests in sensitive individuals and Wolff Eisner [4] in 1906 discussed the possibility that hay fever could be due to a protein sensitivity Since then many workers including Heyl Csonka and others [6] Bernton [7] and Stull and others [8 9 10 11] have extracted active proteins from grass and ragweed pollens The activity has been identified variously in albumin globulin and proteose fractions Much of the early work which used ammonium sulfate or alcohol precipitation actually contained mixtures of various protein and carbohydrate fractions Present day methods using the Tiselius electrophoretic analysis and the ultracentrifuge have given more accurate data Abramson [1] found a single antigen associated with other materials in a hapten like conjugate while Richter Sehon and Rose [13] separated four antigenically active fractions by paper electrophoresis but these were found to be heterogeneous by ultracentrifugation Wodehouse [14 1] using gel diffusion found a major and six or eight minor antigens in each pollen extract analyzed Following the work of Stull Cooke and Chobot [8] the antigens in low and high ragweed were thought to be biologically identical However Wodehouse [18] by gel diffusion studies found the antigens of tall and short ragweed to be not identical but similar *Nevertheless he did find that the six common hay* fever grasses (except Bermuda grass) were practically identical Loveless [17] found that the pH of the extraction media had very little influence on the number of fractions extracted from low ragweed pollen By electrophoretic analysis she was able to show four antigens of different specificity for man Abramson [1] using the ultracentrifuge calculated the molecular weight of a major active fraction in ragweed pollen extract to be 5 000 This has been confirmed by others Since the molecular weights of proteins are 35 000 and more the ragweed fraction is not protein according to the usual standards but is probably a proteose or a polypeptide fragme Winkenwerder Buell and Howard [18] found that ragweed sensit patients gave positive skin reactions to various simple chemi

compounds derived from nucleic acid with normal controls giving negative tests This interesting phenomena has never been confirmed or elaborated upon

CARBOHYDRATES

A carbohydrate fraction in pollen extracts was isolated by Black[19] and Caulfield[9] They obtained materials with over 55 per cent reducing sugars after hydrolysis but the materials also contained from 6 to 1 5 per cent nitrogen These carbohydrate fractions were active when tested on sensitive individuals Harley[1] in England isolated a carbohydrate fraction from timothy pollen which caused only a slight reaction in sensitive individuals in contrast to the great reactivity caused by protein fraction He and many others feel that the reactivity caused by the carbohydrate fractions might be due to contamination with small amounts of active protein The sensitive patient will react to 0 005 mg of nitrogen (equivalent to 1/20 ml of a 0 01 mg total nitrogen or 500 PNU extract) or less A purified polysaccharide (levan—a polymerized fructose) was injected into humans by Allen and Kabat and antibody was produced The antilevan in one serum was partially precipitated by rye grass levan This raises the important question concerning cross reactivity in foods

FAT SOLUBLE SUBSTANCES

Besides the water soluble proteinaceous and carbohydrate fractions which are the main allergenic components in substances inhaled or ingested there is another important class of allergenic substances which may be classified together because of their fat solubility Pollen oils and plant oils including poison ivy are the most common of this group Most of these allergens are contactants in contrast to the inhalants and foods mentioned previously They are generally of low molecular weight and possibly combine with the keratin of the skin to form complete antigens followed then by sensitization of the individual Strauss and Spain[3] prepared a pyridine ivy resin complex which was then alum precipitated for the treatment of poison ivy dermatitis with the idea that a larger molecular and more slowly absorbed allergen would produce a greater immunity Once an individual becomes sensitized to one of these substances he continues to get the dermatitis upon contact with the offending allergen unless treated prophylactically There is rarely a spontaneous loss of sensitivity just as in other forms of inhalant or ingestant allergy

CHANGES IN ALLERGENICITY

There are some proteins of large molecular size which have weak or no sensitizing capacity. This weakness is often thought to be associated with the absence of an essential amino acid. Gelatin is nonantigenic and contains no tryptophane or tyrosine. Ratner and Crawford[4] concluded that soybean is a weak sensitizing protein because of its reduced amount of methionine. Other proteins lose their antigenicity because of processing which causes denaturation. Fries and Glazer[5] showed that heat-processed dehydrated banana could not sensitize guinea pigs as could raw banana and that two atopic children clinically sensitive to banana could ingest dehydrated banana without allergic manifestations. Clinical sensitivity to milk is usually caused by the lactalbumin. Fries[6] showed that it could be rendered relatively nonantigenic by boiling or heating as is done in processing evaporated milk. Lactalbumin is also species-specific so that another mammalian milk such as goat's milk may be substituted for cow's milk. Chase[7] reduced the level of sensitizability of the guinea pig to dinitrochlorobenzene (DNCB) by prefeeding DNCB before attempted sensitization. The clinical implications of this phenomenon are important but have not yet been explored. One wonders if there is any relation between this interesting finding of Chase and the work of Billingham, Brent and Medawar,[8] who showed that embryos or very young animals accept foreign cells or antigens as part of self. They are then not able to form antibodies to them in later adult life (see Chap. 63).

HAPTENS

The broad definition of *antigen* is any substance capable of producing antibodies. An allergen is thought of as any substance capable of inducing an allergic reaction. It is generally felt that simple low molecular compounds are not antigenic since they are unable to form antibodies unless they are bound to proteins or lipids to make larger molecular masses. These low molecular compounds are then called *haptens*, which comes from the Greek haptein, meaning to bind. They are able to combine and bind with antibodies in their low molecular unconjugated form once antibody is formed but they cannot produce antibody of themselves except when conjugated into larger molecules. The conjugation of small molecular compounds such as dyes, drugs (aspirin, thiamin chloride and crystalline antibiotics) and even simple elements such as the halogens, mercury and nickel with proteins of the body to form

cular complete antigens is thought to be the mechanism whereby the human being is sensitized to simple substances Once the antibody is formed the hapten or unconjugated low molecular compound is able to bind with antibody

One reason why it is thought necessary for haptens to be conjugated into larger molecular compounds is that in order to stimulate the body to produce antibodies the antigen must be in contact with the antibody forming cells for a sufficient length of time If the antibody is of very low molecular weight it will be absorbed and eliminated before these antibody forming cells have had sufficient time to have contact with the antigen or to be stimulated by it Therefore the media in which the allergen is carried is important because of its influence on the rate of absorption and elimination

ADJUVANTS

There are several modifications for carriers of antigen so that by prolonging absorption more antibody stimulation is possible and there is less possibility of a constitutional reaction from a high concentration of quickly soluble allergen reaching the sensitized cells at one time These adjuvants include gelatine mixtures [9] alum precipitates [30, 31] and water in oil emulsions [3] to mention a few Freund s adjuvant [33] has been used extensively to promote antibody formation especially in the presence of weak antigens It is a water in oil emulsion containing besides the antigen and mineral oil and aquaphor a suspension of killed tubercle bacillus or *Mycobacterium butyricum* The latter causes a local concentration of a type of cell which along with slower absorption due to emulsion provides more optimal conditions for antibody formation

Recently Rajk and Vinesg [34] combined penicillin with gamma globulin to make more complete antigen for diagnostic purposes in urticaria of the serum sickness type due to penicillin In 34 of 40 cases of penicillin sensitivity positive intracutaneous tests were obtained with the combined testing agent as compared to only 16 obtained with crystalline penicillin alone

Loveless [35] has pioneered in the field of pollen extracts emulsified in mineral oil although Sutton [36] in 1923 first used a repository type of ground pollen in olive oil Loveless has advocated a single injection type of treatment with her pollen emulsion but this is not without danger as was pointed out by Brown [37] who pretreats the patient undergoing such therapy with antihistaminics and epinephrine Large massive single doses are given with this type of

therapy in contrast to the gradual increases in dosage generally ad ministered with the aqueous allergenic extracts

Brown[35] recently reported upon a series of marked local reactions following repository dust emulsion injections One could speculate that this was caused by the patient s being actually sensitized to certain fractions within such a concentrated dust repository extract

CROSS REACTIVITY OF ALLERGENS

The significance of cross reactivity among certain groups of al lergens cannot be overlooked Mosko and others[39] discussed the significance of cutaneous reactions to penicillium penicillin and trichophyton Kagan[40] prepared antigens from *Ascaris* (ascarids from human beings) and from species of *Toxocara* which cross reacted with antibody produced by infections with either species He also showed that *Toxocara* and *Ascaris* whole worm antigens had five to nine common antigen components Campbell[41] isolated a polysaccharide fraction of *Ascaris lumbricoides* var *suum* which could be differentiated serologically from the polysaccharide of ascarids from human beings Loveless[4] in cross neutralization tests indicated that five of the Hymenoptera (yellow jacket bald faced hornet paper wasp honeybee and bumblebee) possessed a common antigenic factor as well as a specific component Weiner and Price[43] showed that a cross antigenicity existed between *Trichinella spiralis* and *Salmonella typhi* Fisher and Shapiro[44] on the other hand ob served 198 cases of nickel dermatitis with positive patch tests to nickel sulfate It is interesting that no cross reaction occurred to potassium dichromate or to copper sulfate

Tuft[45] reported a patient with hypertrophic rhinitis aggravated by the odor of hydrogen sulfide and frying eggs The patient was considerably improved on an egg free diet and when given 1 gm of methionine three times daily showed the same symptoms as with egg This case seemed therefore to demonstrate the correlation be tween the sulfur content of the foods and the tendency to provoke symptoms

COMPLEXITY OF ALLERGENS

The terms *antigen* and *allergen* when used in allergy refer rarely to a single allergen or antigen but to a group of allergens or antigens which are present in an allergenic mass such as the individual pol lens feathers molds or foods These allergenic masses are encoun tered in nature whether inhaled or ingested and are mixtures of

many different individual allergens There are patients who may be sensitive to one major antigenic component to the exclusion of other minor ones and vice versa Since treatment is based upon the fact that some type of immunity is developed because of injections with the specific allergens and since any immune or blocking anti body is specific for the allergen injected it is important to treat with the whole allergenic complex and not with a purified fraction until such a time when it can be demonstrated that antibodies pro duced by a major antigenic fraction will block or neutralize all other fractions

Proteins are readily modified by denaturation but are then still capable of forming antibodies However these antibodies are spe cific for the denatured protein and not for the native unaltered protein All procedures used in the preparation of allergenic ex tracts for testing and treating sensitive individuals must be set up with this in mind Otherwise active antigens may be present but not have characteristics of the original native antigenic mass to which the patient is sensitive Therefore the procedures outlined in the appendix under The Preparation of Allergenic Extracts have been selected for the reason that they cause the least denaturation of the original antigenic material (see Appendix I)

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Bernard N Halpern | 4

HISTAMINE AND PROCESSES OF HISTAMINE LIBERATION

There are few biological substances which have excited such an interest and which have instigated such a considerable amount of experimental and chemical research as histamine

The reason is obvious Histamine is certainly implicated in a great number of elementary physiologic and pathologic processes and particularly in inflammatory reactions[1] However in spite of much extensive and exhaustive study histamine remains a kind of enigma for the physiologist and even more for the clinician

Dragstedt has indicated that the available evidence for the participation of histamine in certain physiologic and pathologic reactions varies from unfounded assumption and illogical inference to substantial and concrete proof

PHARMACOLOGIC PROPERTIES OF HISTAMINE

Histamine possesses the most powerful and diverse pharmacologic properties—too diverse to report here fully

Roughly the main actions of histamine are on the vascular system the smooth muscles and the exocrine glands

It is well proved[3] that histamine is a powerful dilator of the capillaries and in certain animal species (cat dog monkey) and in man histamine dilates the arterioles also This is easy to demonstrate on the blood vessels of the skin Injected intradermally histamine produces a flare and wheal effect which results from the dilatation

of the arterioles and capillaries and the formation of local edema This reaction is often called the triple response of Lewis as it has been carefully analyzed by this British investigator[4]

The dilatation of the capillaries due to histamine is followed by a variable increase in their permeability This results in a loss of plasma fluids through the capillary wall into extracellular spaces and in a more or less severe reduction of the circulating blood volume This phenomenon is one of the elements of histaminic shock

Moreover in man the injection of histamine produces a dilatation of the vessels of the meninges and brain and also an increase of the cerebrospinal fluid pressure The characteristic headache which follows the administration of histamine has been attributed to these cerebrospinal vascular reactions The pain probably originates from stretching of the dural and pial arteries[5]

In dogs histamine produces a constriction of the portal veins which is one of the causes of the resultant systemic hypotension In rabbits on the other hand the fall of the arterial blood pressure seems to be related to a constriction of the pulmonary vessels The diversity of the susceptibility to histamine of the various vascular areas according to the animal species characterizes the peculiar action of this amine

Histamine is a potent stimulator of the various smooth muscles[3] The susceptibility varies largely from one animal species to another The smooth muscles of the guinea pig particularly of the ileum the uterus and the bronchi are sensitive to histamine Striking evidence of the sensitivity of the bronchial tree is the severe bronchoconstriction which can lead to death by asphyxia produced by the inhalation of histamine aerosols by guinea pigs

In human beings the effect of histamine on the bronchioles is negligible in normal persons It produces however a perceptible bronchoconstriction in individuals affected with asthma and emphysema This effect can be observed objectively by the measurement of the vital capacity which is reduced to a variable degree

The effects of histamine on the smooth muscles are easily antagonized by the antihistaminics[6, 7]

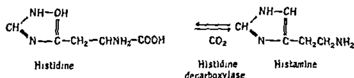
Histamine is a powerful stimulator of the secretions of different exocrine glands The secretagogue effect on the gastric glands is one of the most widespread and specific properties of histamine When large doses of histamine are injected or when injections of histamine are repeated frequently it is possible to produce in animals gastric ulcers and even gastric perforations due probably to the local effect of the highly acid gastric juice The secretagogue effect of histamine is not affected by the antihistaminics

When introduced intravenously histamine exhibits a high toxicity for most mammals Death is due to asphyxia by constriction of the bronchi in guinea pigs to acute dilatation of the right ventricle by pulmonary vasoconstriction in rabbits and to a general vascular collapse in dogs Albino mice and rats are rather resistant to histamine but their susceptibility can be greatly increased by removal of the adrenals [8] or injection of *Hemophilus pertussis* vaccine [9]

ENDOGENOUS HISTAMINE

Histamine is a normal constituent of almost all the tissues in mammals where it is widely distributed [1] Mast cells are probably the source for the bulk of the histamine content of a number of tissues There seems to be a high correlation between the histamine content and the number of mast cells in various tissues [11] However there is definite evidence that histamine is also present in cells other than mast cells

Histamine originates from histidine by the action of a specific enzyme histidine decarboxylase which is present in most tissues



Recent experiments performed with C^{14} labeled histidine have [illegible] firmed this origin [1]

The histamine content varies largely from one tissue to an[illegible] and in the same tissue from one animal species to another [illegible] plete studies of the distribution of histamine in all tissues [illegible] animal species are rather rare In Table 2 are reported [illegible] observations [13] recently made in Wistar albino rats The d[illegible] obtained by chemical extraction of histamine and bioassay [illegible] ing to the technic described by Code Histamine was p[illegible] all tissues studied Skin lung intestinal mucosa and stri[illegible] cles were particularly rich in histamine while the brain [illegible] only traces of this substance

The amount of histamine present in the body is of [illegible] tude that a total release would seriously endanger the [illegible] individual But histamine is stored within the cells as a [illegible] cally inactive precursor Very little is known about t[illegible] nature of this precursor The most likely opinion is t[illegible]

is bound with some acid protoplasmic constituent In mast cells heparin may be the substrate[14] This hypothesis is however far from being satisfactory and therefore one of the essential aspects of the biochemistry of allergic diseases still remains obscure and un solved

TABLE 2 HISTAMINE CONTENT IN THE VARIOUS TISSUES OF WISTAR ALBINO RATS

	μg/Gm	Total tissue content μg/100 Gm body weight
Plasma	0 1	0 4
Blood cells (red white platelets)	0 4	1.6
Heart	8 7	4 3
Liver	3 9	17 9
Stomach *	43 0	25 8
Ileum	13 0	75 4
Colon	10 1	[illegible]0.2
Kidney	4 75	3 8
Skin (abdominal)	8[illegible] 0	1275 0
Lung	9 7	9.2
Brain	< 0.2	
Striated muscle (abdominal)	11 6	5[illegible]2 0
Urine (24 hr /100 Gm)		15 0

* The contents had been removed and the tissue washed

THE PROCESSES OF HISTAMINE RELEASE

Histamine is a highly active and widely distributed constituent of the body to which no physiologic role can be attributed with certainty The amount of histamine present in free form in the cir culating extracellular fluids is exceedingly low in most mammals (2 to 50 μg per liter) and the quantity eliminated daily in the urine of a normal animal (rat) is about 50 to 150 μg per kilogram of body weight But it has been amply and definitely proved that histamine can be released from cells by various pathologic processes and by noxious stimuli of either a physical or a chemical nature

The ingenious studies of Lewis[4] fully established the conditions of release of histamine or of a histamine like substance by injury of the skin which is responsible for the triple skin reaction

One of the most salient problems connected with the release of histamine is the role it plays in anaphylactic shock and allergic reac

tions It was as early as 1910 that Dale and Laidlaw [8] first postulated that histamine might be the hypothetical toxin which Richet [15] had invoked as the possible causative agent of anaphylactic shock The theory of Dale has been the focal point of many investigations too numerous to be summarized here As Goodman and Gilman [16] concluded The net of circumstantial evidence is such that few would deny to histamine an important if not the major role in the charac

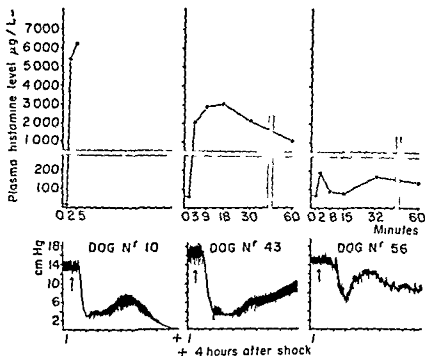


Fig 4 1 Relationship between the severity of the anaphylactic shock and the concentration of plasma histamine in a dog (+ = death)

teristic syndrome of anaphylaxis in certain animal species The main arguments upon which this conception is based are

1 The amount of histamine in the circulating blood is considerably increased during anaphylactic shock and the severity of the shock at least in dogs has a high correlation with the amount of histamine released Figure 4 1 illustrates the release of histamine during anaphylactic shock in dogs and shows the correlation between the severity of the shock and the amount of the plasma histamine [17]

2 Histamine is released from the perfused sensitized organs upon addition of the specific antigen (Fig 4 2)

3 Histamine is released from sensitized cells upon addition of the specific antigen This occurs not only with animals experimentally sensitized but also with human tissues removed from allergic pa tients (Schild *et al* [18])

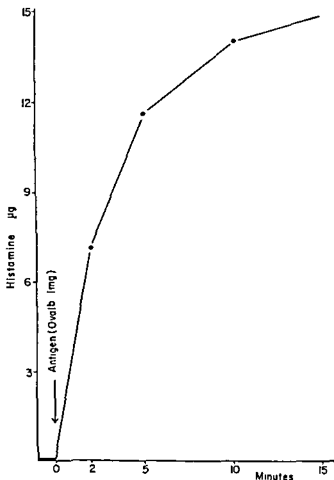


Fig 4 2 Release of histamine from the perfused lung of a sensitized guinea pig after addition of the antigen into the perfusing fluid

4 The histamine releasors reproduce anaphylaxis like reactions in animals and allergy like symptoms in man [17]

5 The potent antihistamines are effective against experimental anaphylaxis and clinical allergies [7]

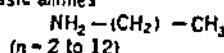
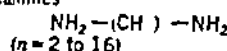
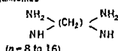
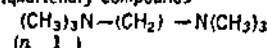
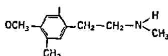
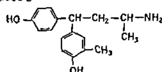
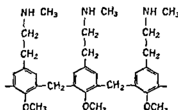
It is therefore beyond any doubt that histamine or a histamine

like substance is released from the cells during the antigen antibody reaction. This does not preclude the possibility that other chemical substances may also be released in these circumstances.

HISTAMINE LIBERATORS

Very similar to the behavior of the antigen antibody complex is the effect of a series of substances recently described as histamine liberators. It is appropriate at this point to stress that many substances possess the property of releasing histamine from the living cells or even from cellular particles. Chemically they are heterogeneous and belong to a large variety of groups[19]. In Table 3 we have summarized the main groups of substances able to release histamine.

TABLE 3 HISTAMINE RELEASING AGENTS

Low molecular weight substances	*High molecular weight substances*
Basic amines  $NH_2-(CH_2)_n-CH_3$ (n = 2 to 12)	Antigen antibody complexes Proteolytic enzymes
Diamines  $NH_2-(CH_2)_n-NH_2$ (n = 2 to 16)	Venoms and toxins
Diamidines  (n = 8 to 16)	Dextran, Ovomucoid } in the rat
Diquartenary compounds  $(CH_3)_3N-(CH_2)_n-N(CH_3)_3$ (n [illegible])	Polyvinylpyrrolidone, Tween 20 } in the dog
Specific compounds 48/80 	Anaphylatoxin, Polymyxins } in the guinea pig
1935 L 	
Alkaloids: morphine, quinine, d-tubocurarine, sinomenine, lichenilormin, etc.	

The classification of the histamine liberators according to molecular weight is certainly arbitrary and does not indicate any chemical relationship Moreover some of the low molecular weight substances show their histamine releasing properties only in vitro while other complex biological compounds such as venoms and toxins possess potent cytotoxic properties in which the release of histamine is more of a secondary phenomenon

The ability to free histamine from its attachment in living cells in perfused tissues or by contact in vitro is rather a common property of many substances On the other hand only a limited number of compounds are capable of producing in vivo the typical and characteristic syndrome due essentially to the liberation of endogenous histamine The substances in this group which have been most studied are 48/80 dextran polyvinylpyrrolidone (PVP) 1935 L sinomenine and peptones It is worthwhile to stress here that the sensitivity of the different animal species to the histamine liberators varies considerably Thus it is quite easy to produce the clinical symptoms indicative of a massive mobilization of histamine in rats cats and dogs while guinea pigs rabbits and mice are more or less refractory Man reacts with a histaminic syndrome to 48/80 1935 L stilbamidine tubocurarine and other substances

The species specificity is even more striking with certain macromolecular substances Thus ovomucoid and dextran act only in rats [9] while Tween 20 [1] and polyvinylpyrrolidone [9] produce the typical anaphylaxis like response only in dogs Anaphylatoxin is the only substance which produces a massive histamine release in guinea pigs [1]

The reason for and nature of this species specificity remain completely unexplained as does the mechanism by which these substances release histamine in living organisms

THE CLINICAL SYMPTOMS PRODUCED BY THE HISTAMINE LIBERATORS

The symptoms vary according to the chemical nature and the dose of the compound and depend particularly on the animal species

In rats the intravenous injection of a large dose of 48/80 1935 L or dextran will rapidly produce symptoms of vascular collapse cyanosis hypothermia and severe hemoconcentration When injected intraperitoneally histamine liberators produce a very peculiar clinical picture generalized itching followed by erythema and edema of the snout tongue and paws Edema hypotension and hemoconcentration signify an increase in capillary permeability This can be visualized by the use of certain macromolecular dyes

such as Evans blue When administered intravenously the dye accumulates in the regions where edema appears and produces an intense bluing of these sites [60]

The intravenous injection of a histamine liberator into an unanesthetized dog produces a dramatic picture In a few minutes there is evidence of intense generalized pruritus The skin becomes erythematous and covered with urticarial blotches Edema is evident around the muzzle and the eyes

In the cat the general symptoms are very similar itching salivation and a state of prostration Later as the animal recovers edema particularly of the nose and eyelids appears A profuse secretion of acid gastric juice is observed If the arterial blood pressure is re

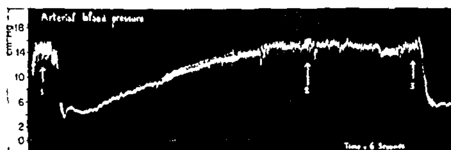


Fig 4 3 Recording of the arterial blood pressure of a dog anesthetized with chloralose The injection at (1) of 1 mg per kg of the histamine releasor 1935 L produces after a latent period of about ninety seconds a sharp fall of the blood pressure The arterial blood pressure returns slowly to the normal level A second injection of the same dose of 1935 L is given at (2) No changes of the blood pressure (refractory state) At this stage the injection at (3) of a high molecular weight histamine liberator polyvinylpyrrolidone produces an intense fall of the blood pressure

corded in the dog or cat a sharp fall of the blood pressure closely resembling that seen with histamine is observed save for a slight difference it occurs about thirty to ninety seconds after the injection instead of being almost immediate (Fig 4 3) The delayed onset signifies that the injected drug does not have a direct effect on the vascular bed but that the pressor response is a secondary process and related to the release of endogenous histamine The delayed hypotensive response is one of the characteristic effects of histamine liberators since it takes time to release endogenous histamine [14]

Histamine liberators and particularly 1935 L have been used in clinical trials [3, 4] When injected into a nonallergic individual a dose of 0 1 mg per kg produces clinical symptoms which are iden

tical with those produced by histamine erythema generalized prickling pulsatile headache fall of blood pressure and gastric hypersecretion All these symptoms are easily controlled by antihistaminics

When 1935 L is injected into patients affected with allergic diseases however quite a different picture is elicited After the first immediate symptoms which are identical with those in nonallergic subjects a second phase of symptoms is observed during which the patient reproduces quite accurately his spontaneous clinical symptoms Patients affected with potential or actual urticaria will re

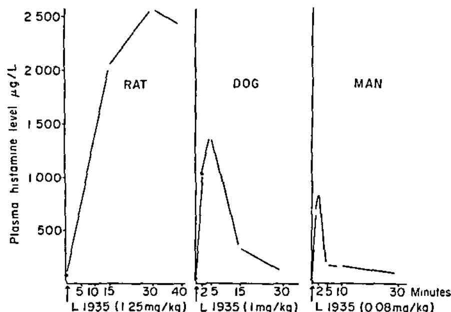


Fig 4 4 Plasma histamine levels after the injection of 1935 L into rat dog and man in micrograms per liter

spond with a severe generalized urticaria but not with asthma In asthmatic patients the same dose of the substance produces an asthmatic attack and only very rarely urticaria In patients affected with migraine typical headaches have been produced

The interesting point is that individuals treated repeatedly with injections of this compound at adequate intervals of time develop refractoriness to the histamine liberator The establishment of the state of refractoriness is paralleled by a considerable clinical improvement in the spontaneous allergic symptoms and it is highly probable that there is a direct relation between the two phenomena [1]

THE DEMONSTRATION AND THE KINETICS OF HISTAMINE RELEASE

The sudden and almost explosive liberation of histamine is reflected by an increase of the plasma histamine level The rise of the plasma histamine after the injection of 1935 L in rats dogs and man is illustrated in Fig 4-4

The release of histamine is rapid and the peak is usually reached within the first five minutes Afterward the plasma histamine level

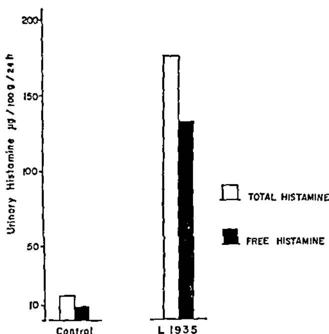


Fig 4 5 Urinary histamine elimination of the rat in control animals and after the injection of 1935 L expressed in micrograms per 100 grams per twenty four hours

decreases slowly but it is not until two to four hours later that it reaches normal values The kinetics of the release of endogenous histamine are closely correlated with the appearance of the clinical symptoms

The release of the endogenous histamine can be proved also by measurements of the amount of histamine excreted in the urine provided that the animals receive prophylactically an injection of a aminoguanidine a specific potent inhibitor of the enzyme which normally destroys histamine in the tissues Figure 4 5 shows the

elimination rate of histamine in the urine in animals before and after the injection of a histamine liberator (1935 L)

Furthermore it should be mentioned that convincing and quantitative evidence for the release of histamine can be obtained by perfusing organs With the usual substances release takes place more readily from the skin preparation and somewhat less readily from perfused muscle In dogs the perfused liver liberates a great amount of histamine with polyvinylpyrrolidone and 1935 L The intestines seem in general to be less sensitive to the histamine releasing action

HISTAMINE DEPLETION AND ACTION OF ADRENAL HORMONES ON BIOGENESIS OF HISTAMINE

By adequate and repeated treatment with histamine liberators it is possible to decrease progressively the histamine content of certain tissues In the rat the skin histamine content can be lowered to about 10 to 20 per cent of its normal content [5] It is very unlikely that the refractoriness to histamine liberators which regularly occurs with repeated injections of these substances is due only to loss of the tissue histamine content

However it has been shown that while release of histamine is an abrupt event the resynthesis of the cellular histamine is at least in rats a rather slow and progressive process [5]

Treatment with cortisone and cortisone like hormones when administered repeatedly is followed by a decrease of the mobilizable endogenous histamine [3] When cortisone is injected into animals whose histamine has been previously depleted by prolonged treatment with a histamine releasor the restoration of the cellular histamine is considerably slowed DOCA has an opposite action [6] [7] (Fig 4 6)

It is likely that the antiphlogistic action of cortisone and its effects in typical allergic conditions are at least partly conditioned by this action on histamine synthesis Very little is known about the stage at which cortisone acts in the cycle of histamine biogenesis

HISTAMINE LIBERATORS AND ANAPHYLACTIC REACTIONS

The injection of histamine releasors is followed in certain animal species by a clinical picture which mimics anaphylactic shock For this reason certain authors have called these effects *anaphylactoid syndrome* [4]

Is the mode of action of the histamine releasors identical with

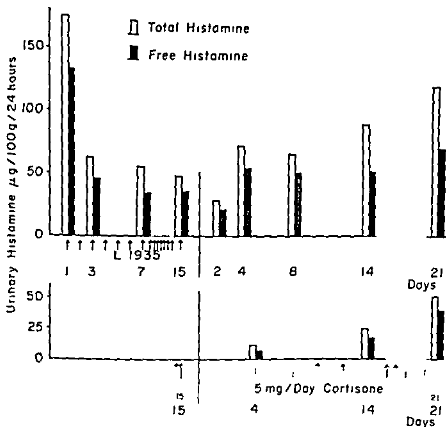


Fig 4 6 The effect of treatment with cortisone on the quantity of histamine excreted in the urine following the injection of 1935 L in animals pretreated with alpha aminoguanidine The columns represent the quantity of histamine excreted in the urine (per 100 grams of body weight in twenty four hours) after the injection of the same dose of 1935 L (*Above*) Due to repeated injections of 1935 L indicated by the arrows the quantity of histamine excreted decreases progressively in relation to its depletion from the tissues At the point indicated by the line depleting treatment is stopped The quantity of available histamine increases progressively Twenty one days later the amount of histamine eliminated in the urine after the injection of 1935 L is almost normal (*Below*) The same depleting treatment with 1935 L is applied to another group of rats Just before the injections of the histamine releasor are stopped the animals are submitted to daily injections of cortisone (dotted arrows) In the cortisone treated animals the quantity of histamine eliminated following the injection of 1935 L is decreased greatly due to a slower restoration of the stock of the tissue histamine

that of the antigen antibody complex? A positive answer would be premature as important discrepancies between the two processes have been found and the matter is still under investigation

The heparin release which occurs regularly in dogs during anaphylactic shock cannot be demonstrated with certainty using the various histamine releasors even with high molecular weight polyvidone

In the rat injection of a histamine releasor is followed by a considerable increase in the plasma histamine content while such an increase has not been found in typical and severe anaphylactic

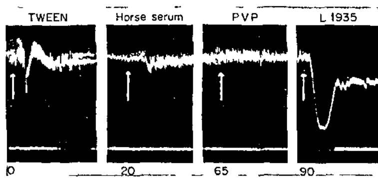


Fig 4 7 Recording of the arterial blood pressure of a dog sensitized with horse serum and anesthetized with chloralose The animal has been submitted for ten days to daily injections of Tween 20 which acts as a histamine liberator in dogs Following this treatment the animal becomes refractory to Tween 20 the injection of which does not produce the usual hypotension The animal is also protected against anaphylactic shock when injected with horse serum (sensitivity to horse serum was demonstrated five days later) The animal is also refractory to another high molecular weight histamine releasor polyvinylpyrrolidone (cross protection) However the subsequent injection of 1935 L produces a definite fall of the blood pressure

shock [9] In this animal antihistamines exert efficient protection against the clinical effects caused by the histamine releasors while they show little effect in anaphylactic reactions Also cross protection against anaphylaxis by previous depletive treatment with histamine liberators regularly fails in rats [30] In dogs such protection against anaphylaxis can be easily demonstrated in animals previously treated and rendered refractory to histamine releasors Figure 4 7 illustrates such cross protection However other facts are in favor of an analogy between the effects of histamine releasors and anaphylaxis Pretreatment with Tween 20 which is a histamine releasor in dogs protects them not only against polyvidone another

high molecular weight histamine releasor but also against anaphylactic shock elicited by injection of horse serum to which the dogs have been sensitized [39]

The action of the various histamine releasors differs however according to their chemical structure Dogs rendered refractory by previous treatment to Tween 20 or PVP may still react to the injection of 48/80 or 1935 L The contrary has also been observed in the author s experiments (Fig 1 7)

This raises the question of the site of action of the various histamine releasors Nishiyama and his coworkers [31] have shown that in dogs compound 48/80 releases histamine mainly from the liver and muscles while Tween 20 polyvidone and sinomenine free histamine essentially from the skin and to a lesser extent from the liver and muscle

Despite some difficulties in the integration of these newly observed experimental facts it can be hypothesized that there are certain basic mechanisms common to the processes by which certain simple chemical compounds free histamine from the tissues and those involved in the antigen antibody reaction The relationship between release of histamine and clinical allergy is stressed by the facts that in allergic individuals the injection of a chemical histamine liberator (1935 L) produces the usual spontaneous clinical symptoms (urticaria asthma) and that refractoriness to the histamine liberator is paralleled by clinical improvement in the occurrence of symptoms These facts also indicate the clinical possibilities of the new series of compounds designated as histamine liberators

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ENZYMATIC MECHANISMS IN ALLERGY

In discussing the mechanisms of allergic reactions it is essential to specify at once the type of allergic reaction being considered This discussion will concern itself with allergic reactions of the immediate type in which circulating antibodies are found These reactions are exemplified by anaphylaxis in the guinea pig and by hay fever and certain forms of asthma in human beings This does not mean that reactions of the delayed type such as the tuberculin type may not be mediated by enzymes It is merely a recognition that the evidence presently available pertains most directly to the immediate type of allergy

The notion that enzymes may be involved in the genesis of the allergic reaction is an old one in fact it is one of the oldest hypotheses evoked to explain its genesis After being more or less discarded it has again become popular In order to understand the modern thinking with regard to this concept however one must understand something of its rather long and involved history

HISTORICAL BACKGROUND

Friedberger in 1909 incubated a washed antigen antibody precipitate with fresh guinea pig serum centrifuged off the precipitate and injected the supernatant serum into normal guinea pigs Shock ensued which had many of the symptoms of anaphylaxis According to Friedberger the shock was due to the in vitro formation of ana

phylatoxin generated by the antigen antibody reaction acting through complement on the precursor of anaphylatoxin present in fresh serum Complement was believed to act by virtue of being a *proteolytic enzyme* The term anaphylatoxin expressed his belief that the signs and symptoms of anaphylaxis were caused by the re lease of the same substance as was formed in the in vitro experi ments Bordet and numerous other authors showed however that not only did treatment of fresh serum with antigen antibody precip itates generate the so called anaphylatoxin but so did agar kaolin and many other substances This led to considerable doubt about the necessary connection of anaphylatoxin with anaphylaxis and led Wells to suggest the use of the noncommittal term serotoxin instead

Also in 1909 Friedmann and Isaac considered that after the inter action of antigen antibody proteolytic enzymes from serum (not complement) are released Bronfennbrenner Jobling and Peterson postulated that the proteolytic enzyme of serum was combined with an inhibitor and thus normally inactive the antigen antibody inter action removed the inhibitor and released the proteolytic enzyme in an active form One of the first ideas as to how the supposed proteo lytic enzyme caused the anaphylactic shock was that toxic material was split off from the protein antigen and it was this toxic material which caused the symptoms and signs of shock When it was found that carbohydrate antigens could cause anaphylaxis this idea had to be abandoned

This entire concept of proteolysis as a cause of anaphylactic shock was severely criticized by numerous workers particularly Dale and the hypothesis was more or less discarded for a number of years These workers pointed out that when isolated tissues such as guinea pig lung or intestine from sensitized animals were washed free of blood a contraction could still be elicited on the addition of anti gen Also there was a widespread doubt expressed as to whether there was any release of proteolytic enzyme during allergic reactions For these reasons and also the concentration of attention on the his tamine theory as *the* causative explanation of anaphylaxis the enzyme theory was almost wholly discarded Roche e Silva however in 1939 showed that trypsin a known proteolytic enzyme on injec tion would yield a shocklike reaction similar in many respects to anaphylaxis and the work of Ungar Burdon Lepow and others has revived the hypothesis[1] In its modern form the hypothesis is that the antigen antibody reaction liberates a proteolytic enzyme which is normally present in an inactive form in serum or tissue cells or both The postulated enzyme breaks down certain specific cells to release histamine serotonin (5 hydroxytryptamine) heparin etc

which cause or contribute to further symptoms In addition the liberated enzyme might directly attack vascular endothelium causing further damage

As pointed out previously it has been shown that injection of certain proteolytic enzymes is capable of giving rise to signs and symptoms similar to that found in the allergic reaction In addition Roche e Silva and Andrade showed that papain (a proteolytic enzyme) is capable of releasing histamine from rabbit platelets indicating that the enzyme theory does not exclude histamine in the development of the signs and symptoms of anaphylaxis

THE THEORY OF PROTEOLYTIC ENZYME ACTIVATION

Numerous investigators have demonstrated increased proteolytic activity in serum following an antigen antibody reaction In addition it has been reported that after the injection of antigen there is an association between increase in proteolytic enzyme activity decrease in proteolytic enzyme–inhibitor activity and presence of anaphylactic shock Ungar[3] has reported a close correlation between the increase of proteolytic activity of isolated guinea pig lung tissue and histamine release

Notwithstanding this and other evidence there is still considerable doubt as to whether the increase of proteolytic activity is the cause of the allergic reaction or merely another manifestation of it playing no real role in the reaction Objections have been raised to the belief that the serum or any enzymes from serum are required for the allergic reactions on the ground that uterine strips from sensitized guinea pigs still give a contraction on the addition of antigen even after the blood so far as one can tell is thoroughly washed out This controversy between the advocates of the humoral and of the cellular genesis of the reaction need not detain us here it is reviewed in detail by Burdon[4] In connection with this point however it is of interest that Hayashi[5] has demonstrated that when monocytes taken from sensitized animals are grown in tissue culture the addition of antigen leads to increase of proteolytic enzyme activity in the fluid surrounding the cells This activity is believed to come from the cells

Nevertheless there still remains room for doubt as to the exact role of proteolytic enzymes in the allergic reaction The only clear cut proof would be the isolation of the supposed enzyme (or more probably enzymes) in the requisite state of purity and the demonstration that this enzyme is capable of being activated by an antigen antibody reaction under conditions similar to those obtaining in the

in vivo allergic reaction In addition it would be necessary to show that this activated enzyme is capable of yielding the same manifestations on injection in the unsensitized animal as is the antigen in the sensitized Th s is as yet an unattained goal In lieu of this sort of proof it is necessary to investigate various models of the allergic reaction and see if they offer any evidence supporting the above or any other theory

The first model to be discussed in this light is that of immune hemolysis the lysis of red cells on the addition of antibody (hemolysin) to the red cells in the presence of complement

MECHANISM OF IMMUNE HEMOLYSIS

It might at first glance seem doubtful that immune hemolysis can serve as a model for the allergic reaction Yet in immune hemolysis one has cell damage caused by an antigen antibody reaction In allergy of the type we are discussing the major focus of our interest is also on the cell damage which is caused by an antigen antibody reaction In the allergic reaction the cell damage is manifested not by the leakage of hemoglobin from the cell as in immune hemolysis but in the release of histamine serotonin etc It does not necessarily follow of course that the cause of the cell damage in one case is the same as in the other but it does offer hope that a consideration of the mechanism of immune hemolysis that is of the mechanism of complement action may shed some light on the mechanism of the more complex allergic reaction In addition there is increasing although still far from conclusive evidence that complement might be implicated in the allergic reaction [6 7]

It has been known of course that it is not sufficient for the antibody to combine with the red cell to cause hemolysis hemolysis requires also the action of complement to be found in fresh normal serum To make matters more complex it also has been shown that complement is not a simple entity but consists of four components all of which must be present and act in a rigidly predetermined sequence in order for hemolysis to occur These components are termed the first second third and fourth components Evidence has recently been obtained that the first component is an enzyme which exists in serum in an inactive precursor form The sensitized cell changes this inactive precursor form of the enzyme to an active form This active form of the first components then participates with the other three components in lysing the cell [1]

The only substrates so far known to be attacked by the first component of complement are esters of amino acids (amino acids com

bined with simple alcohols) Thus the enzyme is an esterase Since these same substrates are known to be split by certain proteolytic enzymes it was suggested that the first component of complement is a proteolytic enzyme As yet however no protein substrate has been found to be hydrolyzed by this enzyme so final proof is lacking Nevertheless the work on complement shows that an enzyme is activated by an antigen antibody reaction and this activated enzyme takes part in the reaction leading to the cell damage caused by the antigen antibody reaction

A model which is more complex than immune hemolysis but in some respects is closer to that of in vivo anaphylaxis is the in vitro release of histamine by antigen antibody reactions Some recent work will therefore be discussed

IN VITPO HISTAMINE RELEASE

Mongar and Schild[8] recently have investigated in some detail the mechanism of histamine release from guinea pig slices by an antigen antibody reaction They concluded that the antigen antibody reaction activated an enzyme which was present in the tissues in an inactive form this enzyme was responsible for histamine release They did not believe that this enzyme was a proteolytic enzyme or was complement The considerations they adduced in support of this disbelief seem however to be hardly adequate for the exclusion of either

Numerous workers have investigated the mechanism of the release of histamine from rabbit platelets by an antigen antibody reaction From these studies it is clear that in addition to the antigen antibody reaction and platelets a factor in plasma is required Humphrey and Jaques[9] have presented evidence for their belief that the plasma factor might be complement and that an activation of a proteolytic enzyme might be involved McIntire[10] on the other hand has concluded that the release of a proteolytic enzyme played no causative role and in fact that the entire process might well be nonenzymatic The most recent work suggests however that whatever the nature of the factor the process does involve enzymatic action[11] This factor too apparently exists in serum in an inactive state and is activated by an antigen antibody reaction[11 1]

Roche e Silva and Andrade have shown that anaphylatoxin or serotoxin as they prefer to call it formed from fresh serum after treatment with antigen antibody precipitate or agar is a potent histamine liberator both in vivo and in vitro They suggested that the activation process might be enzymatic and pointed out that the

in vivo allergic reaction In addition it would be necessary to show that this activated enzyme is capable of yielding the same manifestations on injection in the unsensitized animal as is the antigen in the sensitized Th s is as yet an unattained goal In lieu of this sort of proof it is necessary to investigate various models of the allergic reaction and see if they offer any evidence supporting the above or any other theory

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It is not certain whether this tissue factor is wholly blood borne or fixed on cells or quite possibly both It may well be that complement is the tissue factor involved although this is far from established as yet[1, 8] The evidence that the action of complement involves the activation of at least one enzyme and possibly others has already been referred to

Yet much of the thinking regarding the basic mechanisms operating in clinical allergy has ignored the host or tissue factor concentrating on the antigen antibody reaction for example the explanations that have been offered for the process of desensitization It might well be of value to consider more extensively than heretofore the possibility of exhaustion either generally or locally of the precursor enzyme or increase of natural inhibitors in the process Similarly the question of specific shock tissues always has been troublesome that is the reaction occurring solely or mainly in certain specific sites in the face of circulating antibody and antigens available to all sites Undoubtedly the reasons for this are multiple but attention might well be paid to the possibility of local changes occurring in precursor enzymes and inhibitors as possible explanations

It is possible and even probable that many factors other than the antigen can activate the putative precursor enzyme either locally or generally leading to syndromes simulating that caused by the antigen antibody reaction In many instances of course our inability to demonstrate antibody or obtain evidences of an antigen antibody reaction is due to the inadequacy of our present technics In other instances the possibility should be considered that an *antigen antibody mechanism is not the trigger mechanism* An example of the latter might be chronic urticaria in most cases of which it is impossible to demonstrate an allergen as a causative agent In this instance it might be that something other than the antigen antibody reaction has activated an enzyme system giving rise to the increased capillary permeability which we see as and call urticaria This of course is wholly speculative but it does look forward to the possibility that some day allergy may be defined in terms of the activation of certain specific enzyme systems under certain conditions one being the antigen antibody reaction

The hypothesis of activated enzymes being implicated in allergy also offers hope and promise for a sound and rational approach to the therapy of allergic reactions The work on the mechanism of complement action might well serve as a model for such an approach As pointed out previously it was assumed that one of the components of complement might be a proteolytic enzyme The

further assumption was made that all of the components of complement might be proteolytic enzymes Based on this hypothesis a large series of amino acid derivatives were tested as inhibitors of complement activity In fact certain derivatives were found that would inhibit complement There was sufficient regularity in the structural requirements for such inhibition so that it was possible to predict whether a given amino acid derivative would be an inhibitor If the enzyme supposedly implicated in the allergic reaction can be identified and the type and specificity of such enzymes ascertained it may become possible to synthesize substances capable of preventing their action and thus preventing the consequences of the allergic reaction

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6

AUTOANTIBODIES AND AUTOSENSITIVITY

Soon after recognition of the formation of antibody as a result of the introduction of an antigen such as a foreign protein the question was raised as to whether an animal s own unaltered antigenic constituents can also act as antigens within that same animal Ehrlich *et al*[1] found no evidence of autoantibody formation and formulated the concept of horror autotoxicus Since then much evidence has been amassed to show a production of autoantibody and consequent disease in man and lower animals

Autosensitization is definitely associated with certain diseases and may play a role in others Witebsky *et al*[2] have set forth the criteria to be met to prove that a disease is one of autosensitivity These are (1) the demonstration of an antibody active at body temperature (2) the recognition of the antigen (3) the production of antibody as the result of the antigenic stimulation and (4) the appearance of the resultant pathological changes As yet few conditions have been shown to fulfill all these criteria but one such disease is Hashimoto s struma[3]

THYROID

Early attempts to develop an antiserum against thyroglobulin were not entirely satisfactory because of contaminants in the antigen preparations The first systematic study of thyroglobulin as an antigen was carried out by Hektoen *et al*[4-6] who found that thyroglobulins of several species were antigenic in the rabbit The antisera were not

entirely species specific for they gave cross reactions with thyroid extracts of several though not all species of animals These antisera were however organ specifics for they did not react with extracts of other organs

This problem has more recently been exhaustively reexamined by Witebsky and associates[7, 11] who confirmed the above noting however that anti-rabbit thyroglobulin rabbit serum was not only organ specific but also highly species specific Furthermore not only did they produce homologous antibody—that is antibody against the



Fig 6 1 Example of diffuse chronic thyroiditis of Riedel s type in a woman thirty eight years old Thyroid antibody titer 640 (based on the tanned-cell hemagglutination test) [*Reprinted by permission of the J A M A* 161 1139 (1957)]

material of another member of the same species—but they succeeded in producing autologous antibody—that is antibody in a rabbit formed against extracts of that same rabbit s thyroid

Lesions appeared in the thyroid glands of the rabbits immunized with either homologous or autologous thyroid suspensions In the former group the lesions appeared throughout the gland in the latter they appeared in the remaining half of the gland for in order to autoimmunize it was necessary to remove half the gland suspend it in saline emulsify the suspension with complete adjuvant[1, 15] —that is water in-oil emulsion containing killed mycobacteria—

and inject that emulsion into the animal from which the suspension was obtained The resulting lesions in both groups closely resembled those of Hashimoto s struma [11]

In those animals which developed mild changes most of the gland was well preserved the glandular epithelium was low to cu boidal and some areas of dense white-cell infiltration were seen about the parenchymatous follicles in which little colloid remained In those glands with more severe changes there was marked destruc tion of the follicular organization which was replaced almost en



Fig 6 2 Chronic thyroiditis of the granulomatous (tubercle like) type in a woman forty four years old Antibody titer 40 [*Reprinted by permis sion of the J A M A* 164 1439 (1957)]

tirely by macrophages lymphocytes and plasma cells mostly in nodules bearing a resemblance to lymph follicles In addition the remaining amount of thyroglobulin in these glands was reduced

As yet the relative importance of circulating antibody versus de layed hypersensitivity in the production of these lesions is not clear for often there is no close relationship between the serum titer and the degree of destruction [11] Injection of antithyroglobulin serums should have shed some light upon these problems MacCollum [16] found no lesions in dogs receiving such serums but Lilien [17] believed he produced partial thyroid destruction by such transfer Beebe [18] [3] believed he could effectively treat human thyrotoxicosis with anti–

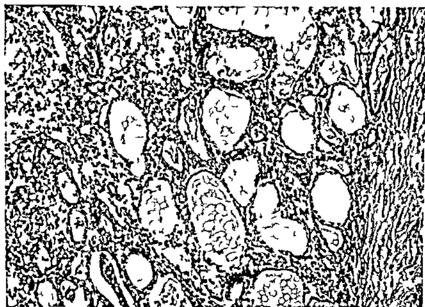




Fig 6 3 *A* Early changes of chronic thyroiditis in a removed left lobe of a woman age thirty-one *B* The right lobe of same patient removed three years later More pronounced fibrosis and lymphocytic and plasma cell infiltration are evident Antibody titer at this time 1 280 [*Reprinted by permission of the J A M A* 164 1439 (1957)]

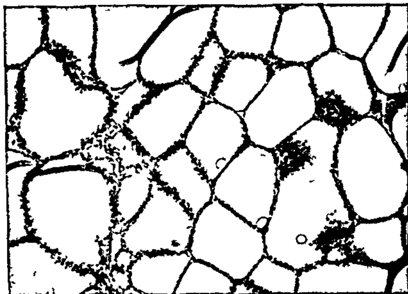


Fig 6-4 Normal control rabbit injected with pooled rabbit serum in Freund adjuvants [*By permission of the Honorary Editors of the Royal Society of Medicine from Proc Roy Soc Med* 50 955 (1957)]

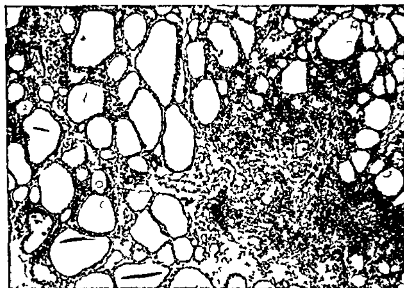


Fig 6 5 Rabbit injected intradermally with 0 2 ml pooled rabbit thyroid crude extract (with Freund adjuvants) on Dec 28 1954 and Feb 22 1955 Sacrificed Apr 11 1955 The figure shows one area densely infiltrated by lymphocytes and eosinophils while the original follicular pattern is pre served in other portions of the section Antibody titer 10 000 [*Reprinted by permission of Cancer Res* 16 831 (1956)]

human thyroglobulin sheep serum and Morgan and Ivy[74] reported the induction of cretinism in rabbits by injecting the young with anti-rabbit thyroglobulin hen serum Such animals were stunted and their hair was shaggy and its growth abnormally slow Further work needs to be done to clarify the roles of circulating antibody and delayed hypersensitivity in the production of disease in rabbits

The striking resemblance of this experimental disease to Hashimoto s struma in man extends beyond the histologic appearance for in patients with this disorder a serum antibody directed specifi

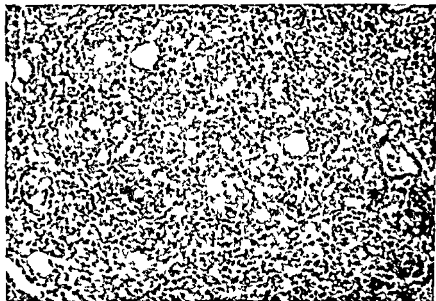


Fig 6 6 Rabbit on same immunization schedule as rabbit in Fig 6 5 Extreme changes with original parenchymal follicular pattern obscured by dense infiltrations of eosinophilic cells and plasma cells Antibody titer 10 000 [*Reprinted by permission of Cancer Research* 16 831 (1956)]

cally against thyroglobulin is present By means of the Coons fluorescent antibody technic antithyroglobulin antibodies have been demonstrated in the glands of persons with this disease as well as in experimental animals [6, 7] The events leading to the production of these antibodies in man need to be elucidated It may be postulated that because of some disorder perhaps a viral thyroiditis malignancy or other disorder the thyroglobulin is introduced into the blood stream from which it is normally absent [8] There it may act as an antigen to cause Hashimoto s struma (Figs 6-1 to 6-9 illustrate clinical and experimental thyroiditis *Courtesy of Dr E Witebsky and Dr N R Rose Buffalo N Y*)

LENS

Just as thyroglobulin appears to be a substance lying within follicles protected from the blood so the substance of the lens lies isolated within its capsule This lens substance was among the first of tissue materials investigated for antigenic properties and was proved to be organ but not species specific [29, 30] Later five antigens were located in the lens of the rabbit one of which appeared in measurable quantity only after birth [31] With the aid of staphylococ

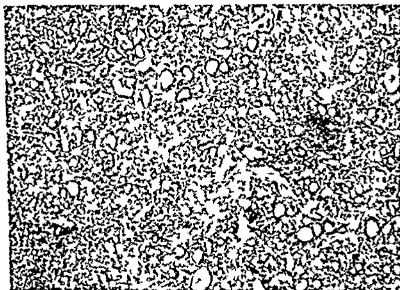


Fig 6 7 Rabbit injected intradermally with 0 27 mg purified rabbit thyroglobulin (with Freund adjuvants) on Jan 6 1955 Sacrificed Mar 14 1955 Acini are small and some are filled with desquamated cells The interstitial tissue is fairly diffusely infiltrated by lymphocytes and plasma cells Slight focal fibrosis around some follicles is also noticeable Antibody titer 2,560 [*Reprinted by permission of the J A M A* 164 1439 (1957)]

cus toxin Burkey produced more potent rabbit antiserums to lens material than had been produced without this toxin

After the animals were sensitized to lens proteins the introduction of a needle into the lens led to severe intraocular inflammation only in those animals which by prior testing manifested skin sensitivity to lens antigen By contrast only mild inflammation developed in response to lens puncture in those animals which had shown negative skin tests and in normal controls [33] The disorder Burkey

felt was analogous to the inflammation seen occasionally in human beings in an unoperated eye after cataract extraction in the other eye This situation termed *phaco anaphylaxis* is thought by some to be a result of sensitization by remaining lens substance following its incomplete removal

The relationship of anti lens antibody and cataracts has also been of interest There seems to be no effect upon an adult animal im

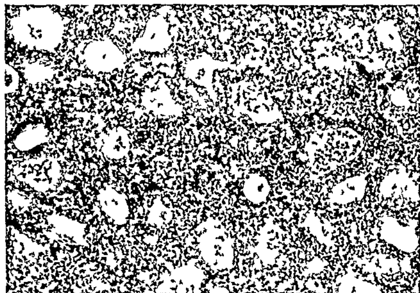


Fig 6 8 Dog injected intradermally with 0 5 ml pooled dog thyroid extract (with Freund adjuvants) on Sept 20 1954 Injection repeated on Dec 21 1954 and Jan 28 1955 Thyroid removed May 23 1955 The section shows dense infiltration of lymphocytes and follicles contain leukocytes and desquamated epithelial cells with little colloid remaining [*By permission of the Honorary Editors of the Royal Society of Medicine*]

munized to lens protein provided that the eye is not irritated However when pregnant rabbits are actively or passively sensitized to lens protein their offspring may develop cataracts[34, 35]

UVEA

Of greater interest and importance is the problem of uveitis Collins[36, 37] was the first to produce experimental uveitis Immunization of guinea pigs with guinea pig uvea emulsified with Freund s complete adjuvant resulted in uveitis as did immunization of monkey with homologous uvea These lesions bear a very close re

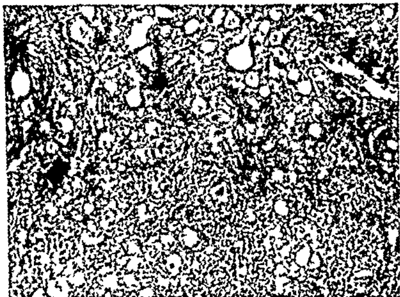


Fig 6-9 Dog on same immunization schedule as dog in Fig 6-8 Dense cellular infiltrations and slight degree of fibrosis evident [*Reprinted by permission of the J.A M.A* 164 1439 (1957)]

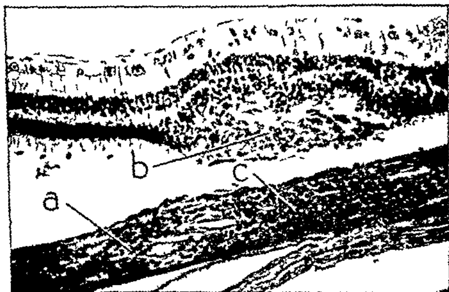


Fig 6-10 Uveitis Area of epitheloid cells in center of nodule in choroid (*a*) proliferation of pigment in epithelium (*b*) area of lymphocytes in choroidal nodule (*c*) area of lymphocytes in choroidal nodule [*Reprinted by permission from the Am J Ophth* 36 150 (1953) *Courtesy of R C Collins*]

semblance to those of human uveitis Other investigators failed to obtain uveitis in guinea pigs although they did obtain complement fixation to uveal tissue and delayed sensitivity to lens protein[38] More recently Bullington *et al*[39] found uveitis in rabbits immunized with optic nerve yet uveal tissue did not cause uveitis when used as an antigen in rabbits[40]

To what extent these lesions result from circulating antibody or a delayed hypersensitivity remains to be shown The relationship of the experimental uveitis on an autosensitivity basis to human uveitis *also must be further clarified*[11] *A discussion of this matter may be* found in the paper by Bullington *et al*[35]

NERVE TISSUE

The previous section mentioned the uveitis produced in rabbits as a result of immunization to optic nerve Disease produced by the injection of extracts of nerve and brain tissue has been the subject of extensive investigation Such a relationship was first suggested by the appearance of central nervous system signs in persons receiving antirabic treatment[41] since then the similarity of the lesions following injections of antirabies vaccine to those of smallpox and measles encephalitis has been emphasized[4 –48] It has been suggested that multiple sclerosis may have an allergic etiology because of its somewhat similar lesions[50 51]

In an attempt to demonstrate that rabbit spinal cord tissue rather than rabies virus caused postvaccinal encephalitis Koritschoner *et al*[5] immunized rabbits with human spinal cord Some developed paralysis of the legs and lesions of the central nervous system resembling the lesions of persons with postvaccinal accidents Experimental proof that lesions with demyelination could be produced in animals was first obtained by Rivers *et al*[3 4] after multiple injections of brain suspension into monkeys Many injections were required to produce signs of nervous disorder and lesions composed of multiple small hemorrhages perivascular white cell accumulation and demyelination *Subsequently with the aid of complete* adjuvants—namely water in oil emulsion containing killed mycobacteria to enhance antibody formation and sensitization of the delayed type—only one injection of antigen was required[6] This advance led to the production of allergic encephalitis in numerous species of animals[5 –6] Variations in the susceptibility of different species to allergic encephalitis as well as variations between strains of one species have been emphasized[63 64]

That allergic encephalitis is a disease of immune response is beyond

question The recently reported[6] production of immunologic unresponsiveness by the injection of central nervous system tissue shortly after birth is additional evidence That toxicity does not account for even some of the lesions of allergic encephalitis is shown by the large amount of antigen that can be injected without effect contrasted to the minute amount necessary to produce lesions if combined with adjuvant



Fig 6 11 Demyelination in the spinal cord of a guinea pig (Spielmeyer stain) [*Reprinted by permission from Arch Path* 50 108 (1950) *Courtesy of J Freund*]

The antigenicity of brain was first demonstrated by Witebsky *et al* in 1928[70] However the nature of the antigen responsible for encephalitis remained in doubt until Olitsky[8] [68] showed that it was within a proteolipid fraction recently obtained by Folch[69]

Except for cross reaction with the testis[9] [71] demonstrated by complement fixation antibody to brain is organ specific yet lacks species specificity The converse also holds true for attempts to

produce allergic encephalitis with organs other than brain fail

The relative importance of the immediate versus the delayed type of hypersensitivity in the production of this disease remains in doubt There is a lack of correlation between circulating antibody titer and the severity of the lesions [9, 61, 65, 1, 3] Because the antigen used for these tests may not be pure and because animals may vary in their response to a given amount of antibody these facts do not exclude circulating antibody as an important agent Nevertheless Freund [9, 6, 63, 4] and others feel that there is a better correlation between the severity of the disease and the delayed type of hypersensitivity

Although attempts to solve this problem by the transfer of immune sera or immune cells have also failed [56, 59] Lipton and Freund [76] have transferred allergic encephalitis in rats by parabiosis In this connection it should be mentioned that offspring of mice immunized prior to pregnancy have an abnormally high incidence of developmental central nervous system anomalies [7]

As shown by Hurst [46] who believes demyelination to be simply a response to any sort of sublethal nerve injury there are many ways to produce demyelinating lesions As a consequence neither the relation between human encephalitis and experimental allergic encephalomyelitis in animals nor the relation of animal central nervous system developmental anomalies to the human anomalies is clear From the above it seems reasonable to believe that human beings receiving antirabies vaccination can develop an allergic encephalitis or ascending paralysis because the vaccine contains the appropriate antigen It should be noted that the lesions in animals with allergic encephalomyelitis are quite similar to those in human postvaccinal disease moderately similar to those of encephalitis due to smallpox and measles and only slightly similar to those of multiple sclerosis (see Chap 36)

TESTIS

Despite a serologic cross reaction between antibody to brain and antibody to sperm [0] immunization with brain does not produce *testicular lesions* Nevertheless *aspermatogenesis and testicular damage* [8, 80] may be produced by immunization with sperm or testicular extracts assisted by adjuvants even when the tissue is taken from the immunized animal This is a specific reaction for the injection of other tissues with adjuvants fails to produce these disorders

In trying to create such lesions Voisin *et al* [81] injected testicular suspensions combined with adjuvants and compared the resultant lesions with those of adjuvant alone Unfortunately the proximity of the injections to the testes produced lesions in those organs as

a result of spread of the adjuvant They concluded that an autoimmune disease was not produced However a study of this problem by Freund *et al* demonstrated that aspermatogenesis could be induced by immunization when injections of testicular antigen and complete adjuvants were made in the nuchal region [8] thereby



Fig 6 12 Aspermatogenesis in the guinea pig [*Reprinted by permission from J Allergy* 28 18 (1957) *Courtesy of J Freund*]

eliminating lesions caused by injection of adjuvant near the testes Furthermore Freund *et al* [60] purified the antigen which appeared to be a carbohydrate associated with amino acids for it was soluble in trichloracetic acid gave a reducing reaction after hydrolysis and resisted boiling Immunization with this antigen resulted in circulating antibody and positive skin reactions Because attempted

passive transfer has failed the relation of circulating antibody and delayed hypersensitivity to aspermatogenesis remains to be proved Nevertheless the delayed hypersensitivity would seem more important than the circulating antibody

This experimental disease in unquestionably one of autoimmunity resulting in sterility It is noteworthy that in the damaged testis the Leydig cells are not affected It is difficult to draw a comparison between the experimental disease and human sterility but the appearance of sperm agglutinins in serum and ejaculate of sterile males is suggestive [8]

BLOOD

In 1904 Donath and Landsteiner [83] found a cold agglutinin in the serum of persons with paroxysmal cold hemoglobinuria The agglutinated cells were lysed by warming the cells to 37 C after the addition of complement In 1908 Chauffard and others [84, 86] suggested the presence of warm circulating hemolysins in acquired hemolytic anemias but evidence to support this hypothesis awaited the development of suitable methods Using the recently devised Coombs test [8] Boorman [88] found globulins on the surface of red cells in acquired hemolytic anemias This finding has been repeatedly confirmed since and extended to other conditions such as a few cases of congenital spherocytic anemia paroxysmal cold hemoglobinuria paroxysmal nocturnal hemoglobinuria many cases of various malignant tumors and lupus erythematosus [89, 91] In some of these the antibodies appear to be the primary agent in others such as congenital spherocytic anemia they are only an aggravating agent when present That these globulins [9, 94] do not combine with the red cells because of altered cell surface properties as occurs in lead acetate poisoning was shown by Kidd [9] From the cells of patients with acquired hemolytic anemia he eluted the antibody which then combined with the cells of normal persons

The specificity of these antibodies has been found to vary from case to case Those from some patients are highly specific reacting with cells of certain Rh groups only [9, 93] whereas those from other patients may be nonspecific—that is they combine with normal red cells irrespective of blood classification [93, 111] These findings suggest that the so called autoimmune hemolytic disorders are indeed diseases of autosensitivity However the antigen has not been identified nor has the disease been experimentally reproduced

It is not necessary to presume that the inciting antigen is the red cell for many naturally occurring substances may induce antibody

formation to human red cells if introduced into other animals.[10 105] However, it has not been shown that these antigens can give rise to autoantibody in humans or in animals.[1 1] Attempts to demonstrate that virus alteration of red cell surfaces can make an animal's own red cells autoantigenic have not succeeded.[1 115] Could it be that these globulins are produced not as a result of an antigenic stimulus but as a result of abnormal metabolism?[111 117] Such an explanation may seem unlikely but certainly has not been disproved.

In addition, a rapidly accumulating body of evidence compiled in recent years suggests that globulins may account for granulocytopenias and thrombocytopenias. Many authors feel that these globulins are also autoantibodies, citing much the same evidence as is used to demonstrate autoantibody to red cells.[11 13] For example, globulins have been found which tend to clump the platelets; they have been eluted from the platelets and used to clump normal ones. Positive reactions to the Coombs test have been found with platelets as well.[1] Nevertheless, by comparison to red-cell agglutination studies the investigations of white-cell and platelet agglutination have not only been far fewer in number but have also been more difficult, for these elements tend to clump and adhere to surfaces spontaneously. Because of these factors, and because the antigen has not been identified or the disease experimentally reproduced, much more work needs be done before these agglutinins can be considered autoantibody.

It should be briefly noted that drug-induced anemias and thrombocytopenias have been thought by some to result from an immune process. Ackroyd[1 8 13] found that the serum globulin fraction of persons with Sedormid purpura agglutinated normal platelets in the presence of the offending drug. Others found a similar phenomenon with serum of thrombocytopenic patients sensitized with quinidine.[131] As a result, it was suggested that an autoantibody to platelets had been formed.[13] Shulman *et al*[133] and others[134] have presented another interpretation; they suggest that an antibody is formed to a hapten such as quinidine. The union of antibody and hapten results in a complex which then clumps platelets because of its surface properties, not because it is an antibody formed as a result of platelets or platelet-hapten combinations acting as antigens. A similar mechanism may operate in certain other drug-induced anemias[18] (see Chap. 10).

Far removed from autoimmunity are diseases resulting from administration of heterologous antisera. An example of such a condition is the nephritis induced by injecting rats with rabbit or duck anti-rat kidney serums[138-139] (see Chap. 38). The basis of a few diseases (such

as allergic encephalitis) produced with heterologous antigens rather than heterologous antiserums may properly be considered as similar to autoimmunization for certain antigens such as the encephalitogenic agent are not species specific but common to several species Therefore immunization of one species with central nervous system tissue from certain other species is very similar to autoimmunization because the tissues of both species have this antigenic constituent in common

When injury is produced by autoimmunization the antigens appear unaltered even when emulsified with adjuvant prior to immunization That antibody so produced combines with tissue in vivo as shown by the Coons fluorescent antibody technic and by the development of lesions is further evidence to support this view

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7 | *Howard G Rapaport*

HEREDITY AND ALLERGY

Heredity has long been considered of great significance in the etiology of allergic diseases particularly hay fever and asthma The tendency of allergic illness specifically asthma and hay fever to occur in families has been reported frequently in medical literature In 1909 Drinkwater [1] described a family in which 10 of 23 individuals in three successive generations had asthma and he concluded from this study that asthma is inherited as a simple mendelian dominant character

Subsequently Cooke and Vander Veer in 1916 and later Adkinson [3] published the results of separate exhaustive studies in which they agreed that genetic influences played a significant role although they disagreed as to how this influence affected the inheritance of allergy The former investigators concluded that hypersensitiveness is transmitted as a simple mendelian dominant character while the latter inferred that bronchial asthma is passed on as a simple recessive trait

In 1923 Coca and Cooke [4] proposed the term *atopy* to clearly demarcate the clinical allergies which were subject to hereditary influence At that time it was thought only human beings could manifest atopy Hay fever asthma and infantile eczema were the clinical illnesses described and classified under the heading of atopy The immediate wheal reaction to skin tests with the antigen and the Prausnitz Kustner reaction of passive transfer ostensibly set this group of illnesses apart from any others of a similar nature noted in other animals Subsequently similar allergic conditions were noted

in dogs and other animals and in addition it was found that immediate whealing reactions and the passive transfer reactions were not always demonstrably positive in humans Therefore the term atopy as originally conceived has proved to be one of limited applicability

Studying the incidence of two allergic conditions asthma and hay fever in the children of families in which one parent or both parents were allergic Spain and Cooke[5] in 1924 confirmed and broadened the observations of Cooke and Vander Veer Assuming that the genetic factor is a mendelian dominant they estimated that when both parents are affected 75 to 100 per cent of the offspring should become sensitive when only one parent is affected 50 to 75 per cent of the offspring should become sensitive and when neither is affected probably 0 to 10 per cent should become sensitive allowing for the possibility of some experimental error The actual data from their studies were close enough to experimental estimations for them to state that the transmitted character was a mendelian dominant

In a clinical review of 285 children with asthma Peshkin[6] in 1928 reported a positive antecedent family history of allergy of 42 5 per cent He also demonstrated that one may obtain a greater incidence of positive family history if one questions parents on a first interview and subsequently one to two years later when the adults have been made familiar with what hay fever and asthma really are Eighteen per cent of family histories that were recorded as negative initially when the patients first came under observation were later changed to positive

In 1936 Wiener Zieve and Fries[7] postulated in a detailed study that allergic individuals may be classified according to the age of onset of symptoms into those who develop first symptoms before puberty and those who do so later those before puberty having bilateral inheritance and those after puberty either unilateral or no obvious inheritance

It has been suggested that a study of monozygotic (identical) twins might shed some light on the subject of inheritance of allergic conditions In other words if allergic conditions are influenced by a hereditary mechanism both twins should have allergy and similar shock organs and allergens should be involved Bowen[8] reported on 59 pairs of identical twins Only seven of the 59 pairs showed dual allergy In the remaining 52 pairs only one of each pair of twins was ill enough to require medical treatment for an allergic disorder

Although the conditions of true germinal or chromosomal inheritance are not absolutely fulfilled in allergic conditions practically

all authors except Ratner *et al*[9] agree with the conclusion that the greater the degree of inheritance (whether bilateral or unilateral) the greater will be the likelihood of the offspring s becoming sensitive

It is likewise agreed by most allergists that one inherits an allergic predisposition rather than a specific allergic disease Descendants of a parent suffering from hay fever may develop asthma or eczema and not necessarily hay fever

Ratner and his associates in particular have questioned the con clusion that inheritance plays a part in the development of the allergic predisposition He reported in an early study (1941) of 250 allergic children and 315 normals that the family incidence was approxi mately the same in both and that about 50 per cent of families in both groups showed no allergy A survey was made in 1952 covering 250 allergic children and their parents and grandparents together with a control group in which Ratner concluded that the incidence in grandparents parents and siblings of allergic children is no greater than in groups of the population chosen at random[10]

Later Ratner and Silberman[11] again reviewed the subject of the influence of heredity on allergy and stated

> We do not imply that we have shown that the gene does not play a role in the production of the allergic state The frequency with which the hypersensitive state occurs in the lower animal and in man makes it extremely difficult to dissociate acquired from genetic factors in its establishment Chromosomal and other factors which may simulate genetic influences require further elucidation

Concerning other factors which may be involved in the produc tion of the allergic state Prigal[1] writes that his studies in which hemolytic coagulase–positive staphylococci were identified and traced by phage typing within a family and interrelated families suggest the possibility that asthma associated with infection and intrafamial contagion may have interfered with accurate determinations of the true role of heredity This he explains was the case with tubercu losis which was considered a hereditary disease because of the high family incidence until the infectious agent was discovered and con tagion demonstrated thus reducing the significance of heredity in tuberculosis (see Chap 21)

Schwartz[13] studying the problem of inheritance in allergy re stricted his field of inquiry to bronchial asthma His intensive clinical and genetic study of 191 asthmatic patients 200 controls and 50 patients with baker s asthma led him to conclude that bronchial asthma is a genetic entity and that a genetic relationship exists be

tween asthma vasomotor rhinitis and probably infantile eczema in which the specific offending allergen is clearly demonstrable His was a statistical study in which the Weinberg statistical genealogic method was used a method which Schwartz considered reliable for the demonstration of inheritance factors He too came to the conclusion that asthma is inherited as a mendelian dominant with failing manifestations so that only 10 per cent who carry the genes would ever develop symptoms

Thus while many studies of an inferential nature have been quoted absolute and incontrovertible proof of the importance of heredity in allergy is not available as has been pointed out In view of this fact it would be advisable to set up a long range project of collecting data relative to this subject [14] There must be many families in which at least a parent or both parents and a child with infantile eczema hay fever or asthma are currently or have been under the care of competent allergists There is the further possibility that three generations may have been or are presently receiving such care If data of this type could be sent to a central clearinghouse possibly an organization such as the American Foundation of Allergic Diseases in a relatively short time invaluable statistics would be easily obtained

The technic referred to previously of requestioning parents several times over a period of years may shed additional light on the history from at least two viewpoints First in the interval someone other than the patient in the immediate family may have developed some allergy and second memories may be triggered by a greater familiarity with the allergic condition

Despite the absence at present of anything approaching a definitive study of the role of heredity in allergy it is nevertheless possible at this point to consider several interesting hypotheses For example there has been a tendency in the past to consider the subject of heredity and allergy in an either/or context—that is the assumption that allergy or the tendency to become allergic is either inherited or acquired Although the majority of allergists have come to accept the former view there nevertheless remains a substantial body of evidence which cannot be fitted to this hypothesis at present Would it not be fruitful therefore to approach the problem from the vantage point of a new assumption namely that allergy can be either hereditary or acquired or both?

Allergists are familiar with cases involving the highly sensitized patient whose allergic symptoms begin at infancy and whose family history has a high incidence of allergy They are also familiar with

patients whose family histories show no incidence of allergy and whose own histories reveal no record of previous sensitization until exposure to large quantities of a specific allergen

In the first case it would appear that allergy was inherited in the other that it was acquired It would moreover appear that the nonallergic individual can be so bombarded with allergens as to become allergic or to use a familiar metaphor that his threshold of resistance to allergens can be crossed provided that the bombardment of allergens is sufficiently heavy If this is true he could be said to have inherited allergy only in the broadest sense of having inherited his general physical make up

One might compare the situation to a river during flood time The houses near the banks of the river will obviously be flooded first but in the event of a major deluge the houses higher up will also become involved Or to use a more familiar analogy one might think of the allergic soil which stimulates the growth of allergy in contrast to the normal soil which unless heavily seeded bears no harvest of allergy

If this is so one can use the term *inheritance* only in the general sense of tendency and one must also provide for the possibility of exceptions i e the precipitation of allergy in the so called normal or nontendency person

By breaking through the heredity vs environment impasse such a hypothesis might serve to focus attention on a more precise understanding of the allergy threshold itself until the statistical picture concerning heredity in allergy is more complete

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Harold A Abramson

8

PSYCHIC FACTORS IN ALLERGY

How far should the general physician go in treating the emotional factors which produce disease in his patients? What is the nature of the problem that the allergist in particular faces? These questions can perhaps be best answered by exploring the nature of the doctor patient relationship in the field of allergy and its significance for the patient and the physician As a background for our discussion let us first take up certain specific factors of some importance in the psychologic management of the allergic patient

SPECIFIC FACTORS

French and Alexander [1] who treated 27 cases of bronchial asthma by psychoanalytic methods found various personality types However they felt that a constant finding was a basic fear of separation from the mother or the mother figure It was suggested that asthma may be the equivalent of a cry of rage or anxiety which has been inhibited or replaced In some cases overprotection by the parents and disapproval by them of psychosexual maturity was believed to be an important cause The psychologic defenses employed by the asthmatic person do not seem to be specific for the allergic disorders because confession conformance ingratiation and utilization of the illness all fit in with the patterns of neuroses found in people who are not asthmatic

Many attempts have been made in recent years to classify the allergic dermatoses on the basis of specific patterns In the experience

of the author the most important factors have been the unorganized and unrecognized rage of the allergic child toward the parent usually of the same sex To identify with this parent means normal psychosexual growth But to identify with someone against whom there is a volcanic inner rage constantly interferes with normal identification processes Without some neurotic utilization of the basic allergic illness this is striving for the impossible This inner rage is turned outward by the patient against himself and leads to a prolongation of the allergic eczema We all have seen the remarkable elimination of allergic dermatoses when the emotional situation is changed In asthma the parentectomy of Peshkin[3] is perhaps an extreme example but does not provide the basic psychodynamic mechanism We know little about the intensity of each of the processes and have much to learn from coordinated studies of allergic and psychic forces

We must never forget that a chronically ill individual is anxious and the treatment of this anxiety is a necessary part of the therapy of the allergic patient no matter how well controlled the immunologic mechanisms may be This anxiety may be expressed outwardly to the physician by the dominant expression of anxiety depression grief hostility phobia or euphoria among other feelings The author has discussed the management of these symptoms elsewhere in detail[4]

In view of the difficulties in giving explicit and specific formulations which satisfy statistical reasoning and the combined experience of both allergist and psychiatrist in allergy I shall attempt to systematize here psychodynamic forces which might be of significance by taking up the general nature of the psychotherapeutic possibilities of allergic patients Generally speaking psychotherapeutic processes may be divided into two types automatic psychotherapy and purposeful or planned psychotherapy which can be further subdivided into (1) reassurance (pharmacologic and supportive) (2) educative with insight and (3) reconstructive psychotherapy with insight

What do all the foregoing groupings mean to the practicing allergist?

THE NATURE OF PSYCHOTHERAPY IN ALLERGY

Automatic Psychotherapy

Automatic psychotherapy begins when the patient decides to seek the advice of his physician for symptoms whether hay fever asthma or any other condition He is seeking to establish a relationship with another person a physician not only trained in the skills of modern medicine but carrying with him the tradition of centuries

of medical learning and interest As the patient enters the doctor s office this relationship continues and is developed through the inter view with the nurse The doctor s assistant is usually a woman and she and the physician play the roles of automatic supporting figures —psychodynamically speaking parental figures—who will listen sympathetically to the complaints of the patient The furniture in the consulting room the credentials framed on the wall pictures of famous physicians of the past and of the present equipment in the examining room all reinforce the automatic psychologic proc esses of therapy that are taking place

As the doctor takes the history—the family history and the personal history—there is demonstrated to the patient that the physician is interested not only in the *things* to which he is sensitive but also without this being explicitly stated in the *people* to whom he may be sensitive All the loves the hates and the anxieties of the patient are directly or indirectly touched on or avoided during the taking of the history The patient realizes that this may be just the beginning of a new and important personal relationship which will help him solve many of his problems not only on a physical level but also on an emotional level

Then bear in mind the psychotherapeutic value of a careful physical examination blood count nasal smear skin tests and other laboratory devices which slowly but inevitably give to the patient an understanding of the nature of his symptoms It is true these are physical procedures but there is an implicit psychologic vector which cannot and should not be underestimated

Then the decision of the physician I recommend that

At last the person with whom the patient has established an im portant new relationship or reestablished an old one gives his conclusions and summarizes what he thinks therapy should be The patient s symptom no matter how trivial or how serious has now become a part of the doctor s life This is an important process which led the patient to share his needs with the doctor and with his other assistants if present The writing of a prescription or the injection of a therapeutic solution may be a physical process but the procedure whether it involves a potent drug or a harmless placebo carries with it the symbolic meaning of the search of one group of men the physicians through the ages for technics to heal the sick

Planned or Purposeful Psychotherapy

Reassurance We have thus far discussed only the automatic psychotherapy which the patient encounters even though the phy

sician is an organicist who does not believe in psychiatry Perhaps the foregoing discussion will enable the strictly organically minded physician to accept the point of view that he is inevitably involved in a psychotherapeutic relationship with the patient no matter how physical his procedures

Leaving this automatic type of psychotherapy I shall now try to show how planned or purposeful psychotherapy may be employed by the allergist in the great majority of cases reserving reconstructive psychotherapy usually psychoanalysis for only a minor fraction of his patients

It should be borne in mind at this point that this discussion does not include psychotic borderline psychotic or near psychotic personality structures This group requires much more complicated management than is usually available in the allergist s office However a certain number of these patients are always found in any physician s practice and it is well to be aware that the automatic psychotherapy procedures are operating even more potently with these patients perhaps than with the nonpsychotic population

Let us now take up a very safe and satisfactory type of planned or purposeful psychotherapy i e reassurance I have previously considered the pharmacologic aspects of this type of psychotherapy as *psychodynamic pharmacology* The recognition that ephedrine and epinephrine may increase the anxiety of the anxious patient and lead to a state of epinephrine fastness the use of chloral hydrate to reduce anxiety the employment of oxygen even though no cyanosis is present the utilization of cortisone not only as an anti inflammatory drug but also to induce euphoria in the asthmatic patient the recognition that amphetamine may aid the eczematous patient to emerge from a depressed state the conscious utilization by the physician of the sedative effect of the antihistamines to ameliorate the anxiety of hives—all combine the best types of medical treatment because the physical and the psychologic aspects of the patient s difficulties are being simultaneously treated by the drugs employed

In this category of planned psychotherapy is the reassurance given to the patient by the physician who will tell the patient that his difficulty in breathing is only asthma that there is no danger or little danger of death that with the administration of antiserum he is fully aware of the dangers of an anaphylactic reaction that he understands the nature of the patient s problems that his allergies are not a disease but a condition that the hives are in all likelihood a transitory phenomenon This is supportive psychotherapy In addition suggesting a vacation new occupational interests or the establishment of new friends and interests outside of self may be

utilized by any physician and applied to a major fraction of his patients There is no danger whatsoever in utilizing supportive therapy of this type Not only does every physician whether psychiatric specialist or not have the right to use this type of therapy but it is his Hippocratic duty to do so within the limits of his knowledge

Educative with Insight The second type of planned psychotherapy depends to a greater extent on the personality of the physician his medical education and his interest in psychotherapy All physicians have had enough training to become appropriately active in educative psychotherapy usually with the development of insight on the part of the patient In this type of psychotherapy the physician sympathetically explores in more detail the personal and family relationships of the patient his work relationships and his position in the community The nature of his difficulties on a conscious level is brought out and problems of adjustment leading to better adaptation may be indicated or planned Readings such as *Emotional Problems of Living* by English and Pearson are suggested and the patient s childhood is discussed in terms of his present adult difficulties In the case of the allergic child more emphasis is placed on the parent child relationship and the problems connected with the establishment of a harmonious home are discussed Helpful are books such as Dorothy Baruch s *One Little Boy* and other works I do not believe however in the theory of maternal rejection as the basic psychologic vector in allergy [5]

This discussion has covered up to this point approximately 90 to 95 per cent of the average allergist s office population It is the responsibility and the duty of the allergist depending on his personality and his interest to understand and to implement as much of the foregoing psychotherapy as he can

Reconstructive Therapy with Insight A maximum of 5 per cent of the allergist s patient population is suited for reconstructive psychotherapy with insight This usually means a psychoanalysis of four hundred hours or more Unfortunate as it may seem not only must the patient have the time and money to undertake this type of therapy but he must also have sufficient ego strength to utilize the revelations of his unconscious Reconstructive therapy should be performed only by those trained in this procedure

Although 5 per cent of the allergist s patient population may be benefited by this type of therapy less than 5 per cent can avail themselves of it Wolberg [6] summarizes the problem by stating that reconstructive therapy is indicated for those whose problems are initiated by severe distortions in parental relations which have pro

duced retardation in maturity The best therapeutic results are obtained with these patients

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9

THE INTERRELATIONSHIPS OF ALLERGY, INFECTION, AND THE PSYCHE A "UNIFIED FIELD THEORY" FOR THE ALLERGIST

ALLERGY Allergy then is a term which should be reserved for over response to an immune reaction It is a kind of stress reaction and as such shares many features with other stress reactions Jensen[1]

When a combination of two or more factors has overthrown the allergic balance the latter may at times be regained by control of one or more without control of all Vaughan[2]

INFECTION All living things from man to the smallest microbe live in association with other living things Through the phenomenon of biological evolution an equilibrium is established which permits the different components of biological systems to live at peace together indeed often to help each other Whenever the equilibrum is disturbed by any means whatever either internal or external one of the components of the system is favored at the expense of the other—and then come about the processes of disease Dubos[3]

THE PSYCHE Man confronted by threats especially as they involve values and goals initiates responses inappropriate in kind as well as in magnitude Such reactions integrated for one protective purpose and thus inappropriately used for another can damage or destroy him Wolff[4]

BIODYNAMICS When (such) a cell is exposed to a repetitive unbalancing environmental action that it cannot avoid its cytoplasmic reaction tends to become disintegrative unless it acquires enzymes that are ade

quate in kind and quantity to produce in time and in form the kind of cytoplasmic responses that will counterbalance the environmental action

Kemp[5]

INTRODUCTION

Both infectious states and psychic factors participate in the production of disease that is commonly considered allergic The role of infection is discussed particularly in Chapters 20 21 24 27 and 52 the role of the psyche in Chapter 8 In this chapter the interlocking roles of all three key aspects of the problem of allergic disease—infection allergy and the psyche—are considered In so doing we may be able to indicate a unified approach which can elucidate the relationships among all three aspects

Regardless of cause all disease can be considered as signifying a disturbance of homeostasis[1] The concept of homeostasis implies a constant interplay of opposing forces which when balanced permit a state of well being but which when unbalanced by one force or set of forces produce a state of disease

Historically this concept was slow in forming Claude Bernard[6] in 1877 considered disease as a disturbance of the internal milieu and Cannon introduced the term homeostasis and discussed its implications in health and disease More recently Selye s studies on stress[8] and the adaptive mechanisms involved which implicate the adrenals have further advanced the concept in physiologic terms Wolff[9] *has made the concept clinically meaningful by conducting* psychosomatic studies of divers diseases including such allergic disorders as urticaria asthma and rhinitis Experimentally he and his associates reproduced these diseases by introducing noxious psychological stimuli and by measuring quantitatively the symptomatic response

Proceeding in Selye s direction Wolff[4] indicated that the very protective mechanism which man employs in his constant need for adaptation may produce disease either because it is called into play when not needed or because in its magnitude and direction the adaptive protective reaction may be more damaging to the individual than the effects of the noxious agent per se (How true this is in allergic practice in which a common food such as egg or milk may produce profound disability or in which a drug like penicillin although given by the multimillion units in septicemia may be lethal when but a few units are given in a skin test) Whereas Claude Bernard considered disease to be a faulty but appropriate adaptive response either hyperactive or hypoactive Wolff showed that the adaptive response may also be inappropriate both qualita

tively and quantitatively He further states Whether appropriately or inappropriately used adaptive and protective patterns operate only in relation to the present in a manner determined by the past and often with dangerous consequences for the future

Bringing the homeostasis concept down to the cellular level Potter and Auerbach[10] consider disease (apart from those following physical chemical or microbiological trauma) a failure or inability of the organisms mechanism of enzyme adaptation * In achieving enzymatic balance a feedback mechanism can be shown in which excess substrate stimulates enzyme production while excess of the product has the opposite effect The mechanism is mediated by the genes This links up with the concept of molecular disease as evolved by Pauling[11] in which disease is due to a hereditary defect in molecules which impair important enzymatic reactions This is considered in more detail in Chapter 63

The interlocking concept of homeostasis stress and adaptation is valuable not only because it is dynamic (and allergy is a dynamic altered *reaction*) but because we are forced to consider mechanisms of interaction i e the interplay of many forces rather than limiting the search to single specific causes for each disease Such a search for a single cause for allergic disease can only lead to a blind alley A single explanation can hardly embrace all the divers reactions encountered (immediate delayed with reagins without reagins divers shock organs etc) In particular the histamine release theory of allergy while still fundamental is limited and cannot explain all allergic phenomena (see Chap 63)

Clinically the allergist who relies exclusively on the skin test without considering the part that infection or the psyche may play in allergic disease is apt to be severely frustrated in his practice Such a practice was in vogue during the earlier days of the specialty of allergy Today one is wise not only to consider whether symptoms might be due to allergy or to infection or to psychological stress (they can arise from each of these) but—infinitely more fruitful—to ask How much allergy? How much infection? How much psychological stress?

The interplay between these divers forces is the subject matter of this chapter Obviously the problem is highly complex since each of the factors comprising it is in itself complex Nevertheless a dia

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* Kemp has recently presented six basic laws of biodynamics which he believes define the reaction of single cells as well as complex organisms in the life process It encompasses the role of genes cytoplasm and the interplay of various forces internal and external which affect *metabolism* These forces can ultimately be expressed in terms of protons and electrons Survival is equated with the ability to adapt

lectic relationship exists among them which can be presented only partially by way of facts The remainder must be theoretical To anticipate and hopefully to counter any objection to such theorizing in a text the eminent Linus Pauling may be quoted A single theory is more important than many facts since it generates action and results in the accumulation of new facts Facts in themselves on the other hand are sterile unless they lead to new theories *

The interplay of these forces (allergy infection and the psyche) is expressed diagrammatically in Fig 9 1 The interrelationship indicated there suggests a dynamic interaction between three complex forces each in itself capable of producing disease In addition since each affects the other each may be able to initiate vicious cycles or chain type reactions Since each is a form of stress perhaps their interrelationship is mediated by the pituitary adrenocortical axis These points are further elucidated following a recapitulation of the places of both infection and the psyche in allergic disease and a brief summary of the relationships with one another



Fig 9 1 Diagrammatic presentation of the interrelationships known or suspected among allergy infection and the psyche Each presumably affects the others The heavier arrows indicate a more positive force (or possibly one more readily recognized or more often investigated) the lighter arrows a less active force or one not so well established the broken arrow a force suspected but not proved (the psyche may modify *symptoms* of allergic patients and perhaps trigger them but no evidence has yet been presented to show modification of the antigen antibody reaction by the psyche)

THE RELATIONSHIP OF INFECTION TO ALLERGIC DISEASE

That infection plays an important role in allergy is generally acknowledged by allergists Its increasing importance as a factor to be reckoned with is reflected in increased discussion and speculation in this book (Chaps 18 20 21 24 27 52 and 62) This is particularly true for respiratory and skin allergies and in cases of asthma rhinitis and urticaria infection must be ruled out as a cause Indeed infection plays a major or contributory role in most cases of asthma and it is probably the main explanation for in

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tractable asthma and status asthmaticus Finke[1] assigns an exclusive role to infection in infectious asthma He deprecates allergic and (presumably) psychic participation His treatment is therefore directed only toward infection for which he advocates continuous and prolonged use of antibiotics often given with steroids Here again is the single cause approach true for some cases but not for all

Nevertheless—and this is most unusual in medicine—we are unable to describe infection in terms of a specific organism Although the author s studies of chronic infectious asthma have most frequently implicated the hemolytic staphylococcus (*Micrococcus* var *aureus* coagulase positive) this relationship has thus far eluded specific identification beyond reasonable doubt[13, 14] Not even phage typing has permitted any implication of a specific staphylococcus[15] For that matter no study has ever successfully implicated a specific organism

Asthma seems to follow any respiratory infection—bacterial or viral and possibly fungal Even though infections such as pertussis measles or pneumonia are most frequently mentioned by the patient as the precipitating cause of the asthma other types of unrelated respiratory infections are also implicated What is the significance of this inability to associate specific infection with allergic disease? Are we to conclude that mere alteration of homeostasis by the stress of any infection may induce allergic disease in those who are susceptible? Perhaps several explanations can be given Before doing so however bacterial allergy will be discussed in deference to those allergists who consider that any infection connected with an allergic disease implies bacterial allergy

BACTERIAL ALLERGY

Bacterial (tuberculin) hypersensitivity was first demonstrated experimentally by Koch[16] in 1891 even before von Pirquet coined the term *allergy* in 1906[17] Two important observations resulted (1) *the Koch phenomenon* an accelerated inflammatory reaction produced by subcutaneous inoculation of antigen in a previously infected and sensitized animal and (2) *the tuberculin reaction* delayed type skin reactions following intradermal injection of the antigen Much later Baldwin[18] observed that aqueous extracts of the tubercle bacillus injected into guinea pigs induced anaphylaxis Rosenau and Anderson[19] using a variety of organisms as the source of antigens had previously demonstrated this immediate type of reaction and had shown that it could be passively transferred Baldwin found however that he could not induce the delayed tuberculin type of

skin reaction without prior infection with the tubercle bacillus and thereby concluded that the delayed type of reaction was a manifes tation of a living infective agent The early widespread belief that passive transfer could not be effected in tuberculin sensitivity was later modified by Chase [0] By using lymph cells of sensitized animals rather than their serum he was able to demonstrate passive transfer in the delayed type of sensitization His success was based on the finding that the antibodies were not of the circulating type but fixed to cells Lawrence [1] demonstrated that tuberculin sensitivity in man could be passively transferred through leukocytes Subse quently Freund Casals and Hosmer were able to induce the delayed type of reaction to tuberculin without concomitant infec tion by incorporating the tuberculin into paraffin oil and so retard ing its absorption

Recently Uhr Salvin and Pappenheimer [3] reported the produc tion of the delayed type of sensitization by injection of insoluble antigen antibody complex The delayed absorption of the antigen plus the inhibition of antibody production by the antibody in the complex results in a delayed type of hypersensitivity The antigen antibody complex is not essential however in producing this type of allergic response

Lawrence [4] has recently reviewed the subject and presented the factors which differentiate this type of allergy from the immediate type of response particularly from the Arthus phenomenon which it closely resembles

In clinical practice aside from the tuberculin reaction the de layed type of bacterial allergy is relatively infrequently encoun tered despite the fact that allergic diseases are so commonly asso ciated with active chronic infection It is noted in addition to tuberculosis in brucellosis lymphogranuloma histoplasmosis and syphilis The acute form of bacterial allergy (anaphylaxis) is a rare clinical phenomenon which has been observed only in the case of tuberculin hypersensitivity Laboratory workers heavily exposed to bacilli or their products (even their odor) have sustained systemic reactions such as chills fever respiratory distress and urticaria [5]

Skin Testing with Bacterial Antigens Attempts to diagnose bac terial sensitization by employing bacterial antigens to reproduce a localized antigen antibody reaction have proved largely unsuccess ful even though the assumption seemed quite logical that the for eign proteins of bacteria could induce allergy in a manner parallel to those of foods inhalants etc Skin testing with bacterial antigens has only led to confusion however since one can obtain both imme diate and delayed types of reactions from antigens derived from the

same source. Furthermore, the reaction obtained can rarely be correlated with clinical findings or cultures, since the positive reaction may reflect a past infection and may be unrelated to the present illness. The clinician is therefore limited to the deliberate production of symptoms by injections of bacterial antigens as the only reliable, albeit limited, means of diagnosing clinical bacterial allergy in the asthmatic patient.[8]

Although it is so very frequently suspected, the proved case of bacterial allergy is infrequently encountered in clinical practice. Perhaps this is a failure which reflects poor diagnostic technics; more refined antigenic agents for skin testing may ultimately be available and prove more fruitful. More likely, it seems that the allergist will have to cling less to this cherished concept of bacterial sensitization and consider more the other roles that infection can play in clinical allergy. These will be considered following some discussion of the relationship of infection to various diseases in which allergy is a known or suspected component.

CLINICAL ASPECTS OF ALLERGY AND INFECTION

Infection and allergy are known or presumed to participate in the etiology of the following groups of diseases:

1. Primary diseases of infection resulting in secondary allergic phenomena. These include the exanthemata and the "ids" as allergic skin reactions, as well as the recognized allergic components of tuberculosis, syphilis, brucellosis, erysipelas, pneumococcal pneumonia, etc. Indeed, it may even be said that no infection exists without some allergic component.

2. Obscure diseases in which an infectious component is suspected but is not yet demonstrable. These include the so-called collagen diseases, rheumatic fever, and the arthritides, and those diseases in which autosensitivity is known or suspected, as in multiple sclerosis, chronic thyroiditis (Hashimoto's disease), the nephritides, etc. In these, the mechanisms of the allergic component is not clearly understood. Suggested explanations include autosensitization or self-perpetuating chain reactions, perhaps secondary to infections.

3. The common allergic disorders in which infection may play a variable role. Clinically, allergy and infection may be noted simply to coexist without apparent interrelationship. Such a situation is exceptional and is exemplified by the asthmatic patient whose asthma remains unaffected by respiratory infection. More commonly the infection and allergy may be additive, as when hay fever or asthma are aggravated by respiratory infection. The symptoms are

compounded by both conditions Allergy as a rule precedes the infection and may possibly make the patient more vulnerable to infection by mechanical and other means which will be discussed later The infection often becomes chronic and may perpetuate the symptoms even though the allergen is no longer in evidence This effect is commonly noted in the postpollen season when hay fever and asthmatic symptoms may continue beyond the time of pollination because of infection Finally a rather large group of patients starts early in life with repeated respiratory infection without obvious allergy only later developing symptoms suggestive of sensitization Although bacterial allergy is suspected in many of these so-called intrinsic cases injection of bacterial allergens will demonstrate this only in a relatively few patients The reverse of this state was recently reported by Rackemann who described 18 patients observed for a minimum of 15 years Earlier in life they had extrinsic asthma from exposure to known allergens and recovered only years later to suffer from the intrinsic type of asthma following respiratory infection He deduced from this that asthma is basically a constitutional disease which may be triggered by two distinct exciting causes (why not both acting simultaneously as may occur in some instances?)

It is suspected at times that infection converts subclinical allergy into clinical allergy implying a preexisting sensitivity to a specific allergen which becomes manifest only in the presence of infection This relationship is not as easily demonstrated as in the case of pollen sensitivity in which the patient notes that during the season he cannot tolerate certain foods or inhalants normally tolerated In addition once such a sensitivity is activated it may continue even after the infection is over

That infection actually induces a completely new sensitivity to foods or inhalants is also suspected at times but is not readily verified Some patients report the onset of clinical allergy to have followed an overwhelming exposure to an allergen—the allergic equilibrium as Vaughan called it becomes unbalanced and hypersensitivity develops more readily Perhaps a parallel imbalance occurs during infection This process is more readily demonstrated experimentally than clinically the rabbit not easily sensitized to ragweed readily becomes sensitized in the presence of staphylococcal toxin[8, 9] The question at once arises of whether or not we are dealing with modifications of homeostasis when we speak of disturbing the allergic equilibrium

Vaughan's concept of allergic equilibrium concerned itself with the induction of allergic symptoms by two or more allergens each

of which in itself was subclinical and did not produce disease Hence the removal of one offender could negate the allergic response to the other If we broaden this concept further to include infection we note that seasonal asthma develops not infrequently in hay fever patients only following an infection and conversely correction of the infection eliminates the asthma and the patient reverts to uncomplicated hay fever

In view of the many clinical entities which demonstrate a variety of interrelationships between infection and allergy the necessity for seeking a single explanation such as bacterial allergy for all of them seems obviated

Experimental evidence demonstrates still other relationships between infection and allergy It has been shown for example that staphylococcal toxin may induce a type of autosensitivity (the Burky phenomenon [9]) and that other infections or agents of infection may enhance sensitivity [30, 31]

Recently it has been reported that pertussis vaccine enhances the induction of experimental allergy [3] Pertussis is now used as an adjuvant in producing sensitization in resistant species (e g anaphylaxis in the mouse or rat) or in enhancing sensitization (e g production of encephalomyelitis by injecting brain tissue extract together with Freund s adjuvant) [33] The mechanism of action of pertussis vaccine has not yet been elucidated Since pertussis prophylaxis in infancy is almost universal in this country one wonders what role if any it plays in the induction of allergy in the human being Moreover one may reasonably assume that if pertussis vaccine (and infection) can produce such profound changes in the immunologic response of the organism other infectious agents and their products can similarly affect it This assumption was recently demonstrated by Malkiel and Hargis [34] who showed that another Gram negative organism *Brucella abortus* behaves like pertussis in its sensitizing properties Certainly this problem needs further investigation

Infection may also simulate the allergic state in other ways as for example pharmacologically Extracts of a pathogenic strain of Staphylococcus can produce anaphylactoid reactions in guinea pig ileum which are indistinguishable from typical allergic muscle contractions induced on an antigen antibody basis [35] This response is not truly allergic but is an allergy like reaction induced solely by the pharmacologic properties of the extract

Possibly this finding can help account for some of the unexplainably severe asthma associated with infection The author has found Staphylococci (hemolytic and coagulase positive) more frequently in

asthmatic patients and in their families than in nonasthmatic control families[13, 14] Since this organism is so ubiquitous being found so often in routine culture from the nose and throat without causing symptoms it is often dismissed as nonpathogenic This error is made because of the failure to recognize that while infection is universal disease caused by infection is relatively uncommon almost accidental and is caused by additional factors modifying the host s resistance[36] that is latent infection is converted under certain conditions into active infection and disease Perhaps preexisting allergy may provide one of these necessary conditions for maintaining infection and for converting latent infection to the active state[3]

Another instance of the complex relationship of infection and allergy is that of an infectious agent H pertussis which is not only capable of inducing disease and sensitization to its own specific proteins but also has the remarkable capacity to enhance the host s sensitization to other antigens as well[3]

Blatt and Nantz[38] have claimed that in infectious asthma specific bacterial filtrates when mixed with the patient s white cells cause their *lysis It is a difficult procedure to perform and perhaps* this has deterred others from employing it Only one other investigator[39] has tested it and found it wanting

Viral Agents and Allergy Viral infections which have become increasingly important to human disease are also implicated in certain problems of allergy However viral allergy is even less well recognized or understood than is bacterial allergy Although some skin testing for viral allergy has been useful many attempts to develop practical diagnostic skin tests (as in viral hepatitis measles mumps etc) have proved unsuccessful[40] Possibly this lack of success may reflect a relative failure of viruses as compared with bacteria to induce an allergic state

In addition it has proved difficult to induce viral allergy in animals because pure viruses have been difficult to obtain Until recently viruses were grown in egg media hence the possibility of the simultaneous production of egg sensitivity was always present When purified tobacco mosaic virus became available recently the author was able to obtain a sample in order to attempt induction of anaphylaxis in the guinea pig Only one of four animals responded in a manner suggestive of mild anaphylaxis although relatively large doses of antigen were used[41] The relatively large molecular weight of this antigen probably required a larger quantity of antigen to induce sensitization

Interest in the role that viruses may play in allergic patients has been heightened by the report of Huebner and his associates[4, 43]

on the presence of adenoviruses as latent infection in the respiratory tract Investigation is needed to determine whether there is any relationship between the adenoviruses—and indeed all viruses—and allergic disease

Clinically it is well recognized but needs emphasis that in the management of allergic patients viral infection of the respiratory tract particularly those of the common cold and influenza frequently stir up the bacterial flora (see Chap 18) Consequently secondary bacterial infection is common and most troublesome since such infection can produce and aggravate asthma It is therefore of practical importance in cases of infectious asthma to prevent bacterial infections by judicious use of antibiotics *during the viral phase* and thereby to avoid the secondary bacterial complications of sinusitis and bronchitis[44]

Diagnosis of Infection As mentioned earlier direct evidence for implicating infection in allergic disease is difficult to obtain Skin testing is notably unreliable and the deliberate induction of symptoms by injection of a specific infectious antigen can only occasionally be demonstrated Thus other indirect evidence must be relied on This includes the history relating symptoms to infection the presence of infection on examination and the favorable response to anti infective therapy In clinical practice one should consider pertinent not only the presence of infection in the patient but also infection in contacts (carriers) as a source of reinfection (see Chap 21)

So complex and dynamic are the forces at work during an infectious process therefore that it is not surprising that the complete relationship between allergy and infection still remains obscure

Diagnosis and treatment of the infectious component in the various allergic disorders is adequately described in chapters previously cited The reader is referred particularly to Chapters 20 21 24 27 and 52

ALLERGY AND INFECTION

We have noted thus far the complex role that infection may play in inducing sensitization Is the reverse also true that allergy modifies infection?

Allergists have noted for many years the vulnerability of the patient with respiratory allergy to sinorespiratory infections They assumed that this infection was secondary to impaired respiratory function (nasal or respiratory blockage stasis of secretions and perhaps modifications of these secretions) That this may not be the case is suggested by the experimental studies of Prigal and Dubos[37]

who showed that a systemic type of sensitization (nonfatal anaphylaxis was induced in the mouse) made the host exceptionally vulnerable to infection with a standard strain of Staphylococcus This is demonstrated in Table 4

Mice sensitized with combined bovine serum and pertussis mixtures became exceptionally vulnerable to staphylococcic infection The animals were challenged intravenously with sufficient bovine serum to produce nonfatal anaphylaxis and simultaneously were infected with a standard dose of staphylococci At the peak of sensitization (23rd day) the infection was at its highest it was most noticeable in the kidneys and was many times more marked than in the nonsensitized mice serving as controls

TABLE 4 EFFECT OF ALLERGIC SHOCK ON FATE OF STAPHYLOCOCCI IN ORGANS OF MICE

Sensitizing treatment * bovine serum (ml i p)	Time (days) between sensitizing and challenge †	No of staph colonies ‡ recovered from individual organs											
		Kidney				Liver				Lungs			
0 5	10	4	14	85		27	39	103		13	22	31	
0	10	0.2	1	12		53	140	118		0.2	2	7	
0.5	18	8	55	160	1 900	21	210	310	1 100	3	6	17	210
0	18	0 1	1	5	35	5	48	56	230	0	0	0 1	2
0.5	23	560	3 200	3,500		78	170	300		0	1	4	
0	23	25	80	750		12	17	47		0 1	1	1	

* All animals received 0 05 ml pertussis vaccine (Lederle) i p
† Challenge infection (i v) 0 1 ml staph culture + 0 1 ml 1/1 000 bovine serum
‡ To be multiplied by 10³ for whole lungs and by 10 for whole liver and kidney
SOURCE After Prigal and Dubos Proc Soc Exp Biol & Med 93 340 1956

Thus a complicated interrelationship may be seen in which infections and products of infection sensitize the host to allergens and conversely prior sensitization impairs the host s resistance to infection *Theoretically it is thus possible to produce by this interaction of allergy and infection a vicious cycle resulting in continuous disease*

THE PSYCHE AND ALLERGY

Considerable evidence exists to suggest a multidirectional relationship between the psyche and allergy In this relationship most authors consider the psyche to be the prime force (psychosomatic

medicine) They claim that the psyche disturbed for some uncon scious reasons uses an organ (the nose lungs or skin) as a voice to express its disturbance and in the process produces allergic dis ease such as asthma hay fever or urticaria[45]

When the approach is Freudian the unresolved conflicts are con sidered to be those between the id trying to fulfill its wishes and the ego the unconscious censor suppressing it Failure at repression of unconscious desires usually psychosexual leads to compulsive behavior This behavior is immature since the driving psychopath ologic force is not understood by the patient and the reaction is unrealistic rather than face and resolve problems he emotes through the physical activity of an organ (see Chap 8) Even the selection of the organ site it is claimed while unconscious is mean ingful Thus asthma is claimed to be the suppressed cry of an indi vidual separated or threatened by separation from the mother fig ure[46] hay fever and rhinitis with its rhinorrhea and sneezing is an attempt to expel a noxious psychologic stimulus and urticaria and itching of the skin are expressions of sexual frustration No at tempt is made with this approach to search for an allergen to con sider an antigen antibody mechanism or an hereditary predisposi tion Nor is the role of infection given any consideration

In considering the validity of this Freudian approach we are forced to admit that unconscious motivating forces are at work in all of us Furthermore psychologic experience can sensitize the brain even as do allergens to selected shock organs or tissues[47] (It might be as important to ask the patient whom he met as what he ate) We can also appreciate the dynamic character of psychosomatic reactions

Nevertheless shortcomings in this approach as well as the lack of familiarity with Freudian concepts tend to make it unacceptable to the average practitioner The explanation of allergic disease on a purely psychological level remains unconvincing and unacceptable because it is so narrow and limited—quite as limited as the approach of the allergist who conceives of disease only in terms of antigen antibody reactions Experience suggests that an either/or approach is unrewarding Possibly consideration of both forces as operating simultaneously or in sequence is more likely to explain the phe nomena encountered Certainly no obvious incompatability exists between basic concepts of psychiatry and allergy

In certain aspects allergy and psychiatry bear a superficial resem blance to one another[47] These two new medical disciplines origi nated at about the same time early in this century Both deal with sensitization which results in one from exposure to an offending

allergen and in the other from psychologic trauma (i.e., an offending experience). Reexposure (to the same allergen or psychologic trauma) produces symptoms which may be either acute and catastrophic or chronically annoying; the symptoms in both are usually out of proportion to the exposure. Both share such mediating chemical agents as histamine, acetylcholine, serotonin, epinephrine, norepinephrine, etc., as recent studies of brain metabolism[49-50] and allergic reactions[51,52] indicate. Finally, antihistaminic drugs, established as being so useful in allergy, have found their way into psychiatric practice as tranquilizers.[53] The parallelism which is indicated by these instances cannot be readily dismissed, even though it may well be argued that it is really unrelated and accidental. Only continued research on a cellular level will ultimately reveal the true nature of the relationship between the two.

Many instances have been established in which a traumatic psychologic experience has precipitated "allergic" disease.[54] Searching deeper, one usually finds that such patients were already allergic, that there was an underlying atopic state, even though psychologic trauma may have provided a precipitating factor. Possibly such reactions should not be termed "allergy," which basically implies an antigen-antibody reaction, but should be considered only as resembling an allergic reaction.

Most often, in clinical practice, the impact of the psyche is noted long after symptoms have been established as allergic. Thus, the individual who already has hay fever or asthma or urticaria caused by specific allergens may find his symptoms to be modified by psychologic stress (this usually aggravates but may even ameliorate). *Such modification is universal, however, and applies not only to* allergic disease but to all types of disease.

Whether or not truly allergic disease can be reproduced psychologically is not easily demonstrable. The common example of the patient with asthma of allergic or infectious origin, whose attack is initiated by psychologic stress, is obviously not demonstrating a strictly allergic reaction in the sense of an antigen-antibody response, since no exposure to an allergen occurred. Possibly the best explanation for this reaction is provided by the concept of conditioned reflexes (Pavlov).[55-57]

Conditioning and the part that it plays in the genesis of disease has unfortunately not received as much consideration in this country as has the role of the unconscious. Until recently, the little that was known concerning conditioning in allergy could be summarized in the finding that the lungs may be conditioned by exposure to proper stimuli in such manner as to alter the respiratory pattern.[58]

and even to produce asthmatoid breathing [57] Now more convincing evidence of conditioning in asthma induced in guinea pigs has been presented by Ottenberg [59] *et al* These investigators induced anaphylaxis and asthmatic breathing by sensitization with egg white and exposing the guinea pigs to an aerosol of egg white solution When these animals were returned to the same aerosol chamber without being exposed to egg white aerosol they reproduced the asthma although less severely than when exposed to the antigen

There is more that needs to be learned about conditioning however In the meantime a rigid either/or approach would again appear to be unwise both conditioning and unconscious motivations could easily play important roles in reversible types of disease such as are encountered in the practice of allergy The two concepts are far from mutually exclusive

Speculation concerning psychologic factors should not be confined to attempts at explanation for puzzling episodes in the treatment of an allergic patient Moreover the physician trained to think in terms of physiology and biochemistry is dissatisfied with explanations which rely solely on abstractions such as ego id instincts unconscious drives etc * Instead he would prefer to recognize the constant interplay between the soma and the psyche as each affects the other in the maintenance and interruption of homeostasis and then seek explanations in the more reasonable and familiar terms of the medical sciences Possibly psychiatry itself is also moving toward such an approach

It is being shown that certain chemicals possess powerful psychopharmacodynamic properties (e g lysergic acid diethylamide) [60] Current intense studies of the tranquilizers and psychic energizers seek to establish not only the nature of the altered psychologic responses but also their actions in localized areas of the brain which induce modifications of brain metabolism [53] The limited form of homeostasis found in the brain itself with adrenergic forces counterbalancing the cholinergic forces provides yet another instance of brain research on a dynamic biochemical level Here too incidentally another resemblance to allergy may be noted since an imbalance between adrenergic and cholinergic forces has been considered a cause of allergic disease

A possible biochemical explanation for psychologic effects in allergic disease may lie in the effect of psychologic stress upon the pituitary adrenocortical axis There is sufficient evidence to indicate that the site of emotional generation is in the hypothalamus and

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* An excellent review of the psychosomatic concept is given by Kaplan and Kaplan [64]

that stimuli generated there affect the adjacent pituitary gland which in turn affects corticosteroid secretion [61, 6] These processes together with the known effects of the steroids on both allergic and infectious processes suggest a resultant interplay of complex forces affecting homeostasis (see Fig 57 2 in Chap 57)

Although no one has actually shown a direct psychic influence upon the antigen antibody reaction such is the possibility since it has been shown that experimental injury in the tuberal areas of the brain prevents or reduces anaphylaxis and this is probably mediated through an interference of antibody production [63] This is an exceedingly important observation and should it be confirmed would once again show the importance of the aforementioned interrelationship of allergy infection and the psyche, encompassing the role of the hypothalamus

ALLERGY AND THE PSYCHE

Not only does the psyche affect the soma to produce a psychosomatic response but the soma distinctly affects the psyche to produce *somatopsychic* responses Thus disease including allergic disease may react upon the psyche and produce psychologic symptoms [47] Moreover a vicious circle may be initiated by the induced psychologic stress (apprehension anxiety and fear of death or disability) which may in turn affect the soma Since somatopsychic reaction is so very common in clinical practice it is just as important to allay the fears of the patient as to relieve his asthma for example In a given situation a kind word may be more effective than a tank of oxygen One may even break the vicious circle by judiciously offered psychotherapy in the form of reassurance as well as by antiallergic measures Preferably one should use both modalities

In the instance just cited it is not the allergic state per se that affects the psyche but rather the physical symptoms resulting from it which can engender such emotions as fear and anxiety Allergy however can also affect the psyche directly as Freeman a keen observer of the interrelationship between the two has noted [64] He believes that this direct effect is demonstrated by the marked changes in mood often observed when allergic patients are exposed to specific allergens without developing overt physical symptoms to account for such behavior In observations made during the hay fever season he noted abnormal emotional reactions coinciding with the onset of the pollen season and terminating with its close One is reminded of the allergic children frequently encountered in clinical practice who are behavior problems until the allergy is properly

controlled at which time they become less irritable and obstreperous. In such instances the allergy seems to have affected the psyche but one cannot be sure of this interpretation since physical symptoms which might engender a psychic response are also being relieved.

There is ample evidence that allergic reactions occur in the brain.[64] Experimentally hemiplegia can be produced in a sensitized animal by direct instillation of the antigen into the motor areas of the brain.[65] Anaphylactic reactions and Arthus type reactions have also been produced[66, 67] as have demyelinating lesions following sensitization by injections of brain tissue extracts.[68] Clinically allergy may induce epilepsy or cerebral edema with a resultant train of symptoms (from simple loss of memory or impaired mentation to loss of consciousness) depending upon the extent of edema.[0] In view of this it is permissible to postulate direct action of allergy upon the psychic component of the brain. A striking symptom terrible fear of impending death is commonly noted during severe anaphylactic reactions to penicillin.[69] Perhaps this may serve as an example of the action of allergy upon the elements of the brain related to the psyche. (The action may be indirect however since so many other events are occurring simultaneously and rapidly which may induce apprehension and fear.)

In considering the interrelationship between the psyche and allergy the effect on the psyche of the medications used to control allergic symptoms must be stressed. One need only mention epinephrine so often used in allergic diseases which is so intimately associated with rage fear or excitement. Less obvious but equally important is the effect on the brain of ephedrine and aminophylline which may induce excitation and sleeplessness. The effect on the brain of the antihistaminics should likewise not be overlooked: they can either depress or stimulate. Undoubtedly the bizarre behavior and emotionalism encountered in some patients is directly due to drug therapy and is therefore iatrogenic and not psychogenic.

Effects on the psyche are also encountered in status asthmaticus owing to the associated anoxia fatigue and dehydration. In short the psyche can be affected in many ways and one should not be too prone to explain symptoms on the basis of a single motivating force. In asthma for example the theme of fear of separation of child from mother has already been cited.[10] More recently maternal rejection has been championed by Miller and Baruch[0] as the psychologic factor most likely to be responsible for asthma in children. On the other hand the parentectomy school of thought[1] advocates

separation of a child from his family as an effective treatment of the severely asthmatic child These concepts have recently been challenged by Harris and Shure [7] and particularly by Leigh [73] who finds no single psychologic mechanism to be consistently involved in asthma

THE PSYCHE AND INFECTION

In the consideration of the interplay of the psyche and infection there is evidence both clinical and experimental that psychological stress is conducive to infection

Although many stresses such as impaired nutrition from war or poverty cold fatigue etc are known to be conducive to a variety of infections the role of psychological stress has been emphasized only recently Under these conditions latent infections are very often converted into active disease Dubos and Dubos [74] for example in their study of tuberculosis have implicated the stress of industrialization upon the high incidence of this disease More recently other investigators [75 6] working with individual patients have implicated stressful life situations as the creators of the necessary soil for the tubercular infection Holmes and his associates [76] noted that a disintegration of the patient s precarious psychosocial environment almost invariably occurred in the two year period preceding the onset or relapse of the disease And to implicate the adrenals a majority of the patients had lower than normal 17 ketosteroids

More pertinent to this discussion however are the observations of Kaplan and Gottschalk [77] who repeatedly observed that the streptococci in the oropharynx increased in a patient when she was under emotional stress but were reduced in number when the patient was calm Perhaps this was due to modification of the pH of the secretions as Fabricant has observed [78] Fowler [79] has also implicated emotional stress in nasal catarrh The classic study however was that of Holmes and his associates [80] from Wolff s laboratory who showed that stresses as divers as exposure to ammonia fumes pollen and anxiety caused hyperemia obstruction increased secretion and increased blood cell count including eosinophils In some instances they even noted asthmatic breathing If continued the process often led to chronic rhinitis cold and sinusitis Abject fear and panic on the other hand led to blanching shrinking and drying of the mucous membranes and wide air passages (probably an epinephrine effect) Here we observe not only the transient effect of the psyche upon the respiratory tract but also that continued stress led to chronic disease states It would have been ideal to have combined these studies with microbiological studies like those of Kaplan and Gottschalk [77]

INFECTION AND THE PSYCHE

The true nature of the effect of infection upon the psyche is difficult to establish Chronic low grade infections (like any other chronic disease) are usually associated with irritability and at times with more severe emotional instability More often this is attributed to factors such as impaired nutrition and loss of weight fatiguability and perhaps frustrations arising from inactivity or inability to perform at full capacity But since infection implies the presence of multiplying living organisms it is also conceivable that in their metabolism they secrete noxious agents acting directly on the psyche In the case of tuberculosis it has been claimed that owing to a toxin the victim remains unaware of the seriousness of his illness (*Spes pthisica*) Berle [5] explored this concept and found it invalid

In acute and overwhelming infections toxic action on the brain is strongly suggestive since the delirium frequently encountered is like that seen in the psychoses induced by the halucinogens The delirium is usually associated with the febrile stage of the disease the higher the fever the more likely the delirium Nevertheless delirium may occur either before the onset of fever (initial delirium) or after the fever [1] The occurrence of delirium during those afebrile periods is strongly suggestive of a toxic reaction on the brain On the other hand one may encounter stuporous states as typified by typhoid fever Since these infections are usually widely disseminated direct invasion of the brain resulting in impairment of its functions including emotional reactivity may be postulated This is not necessarily so since even typhoid vaccine can cause depression and lassitude

Since some infections have a predilection for the brain or its coverings the encephilitides and meningitides are expectedly associated with a variety of psychologic disturbances The psychoses of infection are stated by some to stem from the toxic action of the infective agent either acting upon the cortex or suppressing the usual inhibitive forces Others state that like the halucinogens they act upon the reticular activating system in the hypothalamus [8]

Experimentally it has been shown that infection with herpes simplex can be modified by stress Following the clinical observations that herpes simplex the most ubiquitous of all virus infections in man was related to psychologic stress [83 84] Rasmussen Marsh and Brill [8] applied two forms of stress (electric stimulation and rigid confinement) to mice and then infected them with the herpes virus The stressed animals had a higher mortality rate than did the control group of unstressed mice infected in the same manner In addi

tion a shorter survival time was noted in the mice subjected to stress

VICIOUS CYCLES SELF PERPETUATING REACTIONS CHAIN REACTIONS

Before concluding this discussion on the interaction of allergy infection and the psyche encompassing the role of the hypothalamus a brief consideration will be given of the possibility that chronic or recurrent allergic disease may occur because these interactions provoke chain reaction mechanisms or vicious cycles or set in motion self perpetuating forces For example since infection is conducive to allergy which in turn is conducive to infection which is conducive to allergy etc a vicious cycle can be initiated The other members of this triumvirate of stresses in varying combinations may perhaps also be capable of inducing self perpetuating reactions * It may very well be that we are dealing here with the same type of feedback principles as those that are encountered in cybernetics [1]

A mechanism involving a chain type reaction is suggested by Pappenheimer as an explanation of a delayed type of allergy

It is postulated that leukocytes of sensitive individuals contain in their surface structure a type of cellular antibody with a high affinity for antigen Combination with antigen possibly mediated by complement results in the release of the cellular antibody (transfer factor) antigen complex The antigen antibody complex subsequently disassociates and liberates the transfer factor and free antigen Other sensitive cells may be damaged by combination with dissociated antigen and nonsensitive cells attracted to the area may engulf the transfer factor thereby becoming sensitized themselves In this fashion a progressive process is set in motion which will continue until antigen is exhausted [86]

Multiple sclerosis [68] may provide an example of what may be an allergic disease possibly caused by a self perpetuating mechanism Experimentally brain tissue whether homologous or heterologous

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An example of a mechanical self perpetuating mechanism is the noise produced when the receiving end of the old fashioned telephone is sharply placed against the speaking end The noise from the contact is magnified by the speaker and becomes louder in the receiver is further magnified etc until an eerie howl is emitted A medical example of vicious cycle reaction is that encountered in the shock associated with myocardial infarction Shock may be caused by peripheral vascular collapse or by heart failure or by both one inducing the other Pain and tissue destruction can produce peripheral shock Prolonged hypotension in turn results in coronary insufficiency and secondary myocardial infarction further aggravating the shock further aggravating the coronary circulation etc

has been shown to produce upon injection an allergic encephalomyelitis resembling multiple sclerosis Since brain tissue is allergenic destruction or injury (perhaps from infection) may produce antibodies which when combining with the antigen may in turn produce tissue damage in the brain liberating more antigen etc In addition to the brain the testes liver kidney thyroid and perhaps other tissues or organs contain suitable antigens Thus a self perpetuating mechanism may perhaps be applicable to any disease of autosensitivity (see Chap 6)

THEORY OF CAUSATION OF ASTHMA AND OTHER ALLERGIC DISEASES

Throughout this chapter it has been stressed that asthma is a symptom complex resulting from the interplay of many forces internal and external As disease arising from infection it involves an interrelationship between the causative agent or agents and the host or patient Basic to all asthma is a variable constitutional predisposition The greater the predisposition the fewer forces (and smaller exposures) are needed to trigger asthma This is the truly allergic (atopic) asthma encountered early in life and caused by specific allergy When the predisposition is mild many forces acting simultaneously or in sequence are needed to impair homeostasis—here allergy infection and the psyche working together or in sequence tilt the scale of allergic balance Here time is also an important factor—time to develop reactivity to these forces—and therefore this type of asthma arises later in life In between these two ends of the asthmatic spectrum are the patients of moderate sensitivity who may require two factors (allergy and infection or allergy and psychological stress) to precipitate symptoms

To these relatively simple aforementioned mechanisms must be added the dialectic interrelationship among allergy infection and the psyche previously discussed which probably accounts for variability of the patient s responses to allergens infection or psychological trauma The chronicity is explained by the existence of self perpetuating mechanisms (infection is a form of self perpetuation) or vicious cycles resulting from the modification of each of these forces by the other These vicious cycles may at times be broken by attacking therapeutically only one of the three stress forces Thus, the allergist may discover a potent allergen and remove it and the homeostasis is restored Or an infection may be adequately treated and the patient improves despite exposure to known allergens or to psychological stress Or if the latter is an important factor and is corrected by psychotherapy the cycle may also be disrupted by this

means to restore homeostasis In most instances however the single approach along only one of the three avenues indicated above is inadequate or may provide only temporary relief The same approach applied to the causation of asthma applies as well to other allergic states such as hay fever urticaria and eczema

In conclusion then although much remains to be learned about the interrelationship between allergy infection and the psyche sufficient information exists to indicate the wisdom of the over all approach in clinical practice Certainly it is more fruitful for the patient and the physician

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10

PATHOLOGY OF ALLERGIC AND COLLAGEN DISEASES

The study of the pathology of allergic diseases runs at once into the difficulty that no satisfactory definition of an allergic disease is available Indeed it seems better not to speak of allergic and nonallergic diseases at all but with Cooke to specify the allergic component in diseases as minimal or absent in some predominant in others and anywhere in between in the remainder A glance at the chapter headings in this book will reveal the marked extension of the idea of allergy far beyond the confines usually thought to be the allergist s domain

Whatever else it may be the allergic response is a way the body reacts to certain stimuli Whether this way of reacting always has an antigen antibody reaction as its eliciting cause remains to be seen it is suggestive that reactions which had seemed difficult to subsume under this heading have increasingly found room there for example the haptenes of drug reactions and the autoimmune states From the pathologic anatomic point of view however none of the reactions are pathognomonic all of them occur in nonallergic states This is not equivalent to saying that the histopathology of allergic states is unknown or that it is unimportant It does mean that the final determination as to whether a condition is allergic can be arrived at only after the histologic data are correlated with clinical physiologic and immunologic data

When the whole field of allergic and related conditions is surveyed a striking phenomenon appears All the pathologic types we

shall describe tend to appear in some degree or in some instances in all the conditions together with certain clinical and immunologic factors which include plasmocytosis hyperglobulinemia dysproteinemia cryoglobulinemia and others This overlap tends to show that these conditions share pathogenic mechanisms which is just what we should expect if they all have an allergic component At first glance this may seem to lead to a complete confusion in pathology Fortunately there is a way out If we adopt as our guiding principle the *dominant* histologic finding we come out with relatively few groups of pathologic conditions (Table 5) Furthermore these groups show numerous correlations with clinical and immunologic data (Table 6) On the whole it offers a satisfactory classification from the pathologic point of view The fact that some conditions belong at times in more than one class is easily understandable

All the above considerations may seem dogmatic and indeed almost have to be when given in summary Their backgrounds and reasons are given in the papers referred to in the bibliography which also furnish the references for what is to follow

It is obviously impossible to give in detail in so short a space the pathologic basis of all these conditions Emphasis will therefore be placed on the general features

NECROTIZING LESIONS

Necrosis in some form is likely to be present in all the kinds of allergic tissue changes except in some of the hyalinoses Its location within the lesions and its type helps differentiate many of the lesions as will be seen below Here we shall consider the diffuse necrotizing lesions which come on suddenly involve much or all of a tissue—the renal cortex (Fig 10 1) or the pancreas for instance—or a single type of cell such as blood platelets There may be considerable inflammatory reaction at the periphery of the lesions or death may come so rapidly (or occasionally an organ be removed surgically) that the necrotic area ends abruptly with no peripheral reaction Many of the lesions are hemorrhagic because of the disruption of blood vessels by the necrotizing process Both anatomically and pathogenetically these lesions resemble the Schwartzman and the Arthus reactions of experimental medicine

The process may not be diffuse in an organ but may select a single element or even a single kind of cell In this group are lesions which are thought to be autoimmune processes (see Chap 6) such as thrombocytopenic purpura the demyelinizing neuropathies perhaps even hemolytic anemias and granulocytopenias Some of the

diffuse necroses may also be on an autoimmune basis Perhaps this explains why cortical necrosis of the kidneys is usually bilateral Previous damage to the involved organs can often be found and this may be the evidence for the mechanism by which the autoantigen was originally absorbed In cases of acute hemorrhagic necrosis of the pancreas for instance there are nearly always small connective tissue scars in which acini have disappeared and only a few islets remain

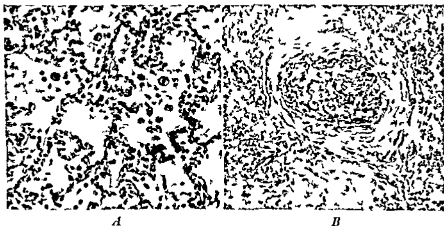
TABLE 5 HISTOLOGIC CLASSIFICATIONS OF ALLERGIC LESIONS

Type of lesion	Examples in human pathology	Examples in experimental pathology	Nonallergic mechanisms which may produce changes
Necrotizing			
Tissue selective	Cortical necrosis of kidney acute pancreatic necrosis	Arthus and Schwartzman phenomena	Primary drug injuries
Cell selective	*Thrombocytopenic purpura granulocytopenia*	Antiplatelet serum	Primary drug injuries overwhelming infection
Anaphylactoid	Serum sickness asthma and hay fever atopic dermatitis glomerulonephritis periarteritis nodosa	*Experimental anaphylaxis experimental nephritis etc*	All the mechanisms producing stress (Selye)
Granulomatous			
Tuberculoid	Tuberculosis brucellosis tularemia beryllium granulomas	Experimental infections with same organisms	*Probably* none
Rheumatoid	Rheumatic fever rheumatoid arthritis Giant cell rheumatoid granulomas	?	The mechanisms of stress and the diseases of adaptation (Selye)
Hyalinoid			
Collagen diseases	*Disseminated* lupus erythematosus dermatomyositis scleroderma	None known	The mechanisms of stress and the diseases of adaptation (Selye)
Amyloidosis	Amyloidosis	Parenteral injection of proteins or nucleic acids	Neoplasms (multiple myeloma) others?

TABLE 6 CORRELATION BETWEEN HISTOLOGIC CLASSES AND CLINICAL AND IMMUNOLOGIC PHENOMENA IN ALLERGIC DISEASES

Histologic class	Type of clinical reaction	Clinical course (velocity)	Duration	Skin reaction	Antibody in serum	Increased serum globulin	Specific infection	Eosinophilia	Necrosis
Necrotizing	Immediate	Rapid	Short	0 or + necrosis	0 or +	0	0 or +	0 or +	++++ (diffuse)
Anaphylactoid	Immediate	Rapid	Short to moderate	Wheal type	Frequently +	Usually 0	0	+ to ++++	+ (fibrinoid)
Granulomatous									
Tuberculoid	Delayed	Variable	Short to long	Tuberculin type	0	0 to +++	+	0	++ (caseous)
Rheumatoid	Delayed	Slow	Long	0	0	0 to ++	0	0 or +	++ (fibrinoid)
Hyalinoid									
Collagen diseases	Delayed	Variable	Short to long	0	0	++	0	0 or +	++ (fibrinoid)
Amyloidosis	Delayed	Slow	Long	0	0	+ to ++++	0	0	0

Fig 10 1 Acute hemorrhagic necrosis of renal cortex *Bacillus pyocyaneus* infection with sharp border between necrosis on left, and normal renal tissue



A *B*

Fig 10 2 *A* Anaphylactoid edema of lung area in case of status asthmaticus The ability of the edema fluid in the alveoli to stain depends on its high protein content *B* Isolated lesion of necrotizing arteritis in the kidney anaphylactic death following penicillin injection

ANAPHYLACTOID LESIONS

The majority of the diseases seen by the practicing allergist fall into this group For this reason and because anaphylactoid lesions may accompany most of the other allergic lesions this reaction deserves extended consideration

In general whether an anaphylactoid lesion is fatal or is quickly reversible and relatively harmless depends not on differences in the kind of lesion but on their location and extent Thus the pathology



Fig 10 3 Polypoid lesion of nose in case of allergic rhinitis A Marked edema (low power) The spaces are in part dilated lymph vessels in part tissue spaces The scattered cells are mostly eosinophils There is hyperemia just beneath the epithelium B Eosinophil cells (rounded cells) wander through the intact but somewhat edematous epithelium toward the lumen (high power)

of a hive and of angioneurotic edema of the glottis is essentially the same Both are essentially simple edemas (Fig 10 2) (See Chap 2)

There is a group of cases however in which death in what seems to be anaphylactic shock is so sudden that there are no pathologic findings of any kind When the time which elapses between the giving of the fatal substance and death is considered it becomes unreasonable to expect that there will ever be any characteristic anatomic finding Recently in a case of death within seconds after an injection of penicillin there was found after prolonged and careful search a single arteritic lesion in a kidney (Fig 10 2) This was of

course not the cause of death but it constitutes evidence for the existence of a state of hypersensitivity

A simple edematous lesion is seen in Fig 10 3 from a case of *allergic rhinitis* Beneath the epithelium connective tissue fibers are separated by large amounts of edema fluid containing a few inflammatory cells mostly eosinophil leukocytes Eosinophils migrate through the epithelium to the lumen where they may be found in nasal smears to aid in the diagnosis This simple reaction is with modifications the basis for most anaphylactoid lesions An *urtica*

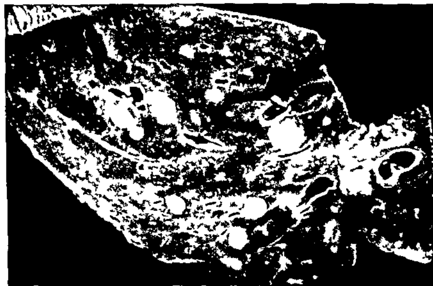


Fig 10-4 Lung in asthma extreme instance of plugging of bronchi Very small branches of the bronchi have become visible because of the dilatation and plugs of mucus

may not have the cellular infiltration It should be remembered that the lesion in Fig 10 3 is a chronic one In recent edematous lesions the methods of tissue preparation may cause disappearance of all fluid so that what looked like a severe lesion to the clinician will appear like normal tissue under the microscope Asthma has been called urticaria of the bronchi

Asthma The characteristic findings in the asthmatic lung are four in number and their presence makes it possible to recognize the asthmatic lung without a history or a clinical diagnosis (1) The bronchi are dilated and filled with plugs of inspissated mucus (Fig 10-4) When the patient dies in status asthmaticus this may involve



Fig 10 5 Asthma a medium sized bronchus mucicarmine stain Almost every lining cell has been converted into a mucin producing goblet cell The mucin is the black-dotted material within the ellipsoid goblets Normally only a few of these cells would be mucin producing



Fig 10 6 Asthma a focus of squamous metaplasia in a medium sized bronchus Beneath it is a thick hyaline deposit Notice especially above and to the right that this seems to be not a thickened basement membrane which can be seen distinctly but a deposit beneath the membrane

every bronchus and bronchiole to an extreme degree or when an asthmatic person dies from some other cause it may affect only a few bronchi (2) The number of mucus producing cells in the bronchial mucosa is markedly increased (Fig 10 5) Mucus threads in the lumen may be anchored in the goblet cells of the mucosa There is often increased mucin production by bronchial glands and their openings into the lumen of the bronchus may be dilated (3) There is a deposit of hyaline material on and beneath the basement membrane of bronchial epithelium (Fig 10 6) When the microscopic preparation is not carefully made this may appear as the thickened basement membrane frequently described (4) There are foci of squamous metaplasia (Fig 10 6) Such metaplasia is not rare in normal lungs In adults it may be found in 15 to 20 per cent the greatest incidence being in lungs with chronic infection with much lower incidence in childhood In the lungs of asthmatic persons it is present in the vast majority of cases and is just as frequent in children

Segments of bronchiolar mucosa show the urticarial lesion described above and they may be the sites of marked eosinophilia In people who die in status asthmaticus there are often patches of anaphylactoid edema (Fig 10 2) characterized by infiltration into the alveoli of edema fluid with high protein content which therefore stains with the ordinary dyes used Full blown polyarteritis nodosa occurs in a very small number of asthmatic subjects but a few foci of arteritis are seen more often Secondary changes such as purulent bronchitis are uncommon emphysema depends on the obstruction by mucus plugs and is most common in older persons

Allergic Pulmonary Infiltrations Several pulmonary parenchymal infiltrations are known *Rheumatic pneumonitis* involves the middle segment of the lung and tends to be very hyperemic or even hemorrhagic Small patches of granulomatoid infiltration are common in fatal drug hypersensitivities *Loeffler's transient infiltration* is characterized in the few fatal cases which have been studied anatomically by an anaphylactoid pulmonary edema and intense eosinophilic infiltration Similar focal anaphylactoid lesions without eosinophilia are seen in acute disseminated lupus erythematosus sometimes called *lupus pneumonitis* The edematous infiltration about a focus of tuberculosis called an *epituberculous* lesion is anaphylactoid

Arteritis It is now established beyond doubt that most instances of necrotizing arteritis are the result of localization of antigen antibody processes in arteries The experiments of Rich and his associates who produced characteristic lesions in animals which had

received great doses of foreign protein were the climax to a wealth of clinical and histologic evidence What is not so clear is whether all necrotizing arteritis is allergic and whether cases of nonnecrotizing arteritis may also be allergic There are two general schools of thought on this matter One sees different distinct entities in the several forms of arteritis Zeek whose classification is the most workable divides them into five distinct forms The other assumes that all the forms may have the same or similar origin but vary depending upon the amount or the rate of involvement This presentation

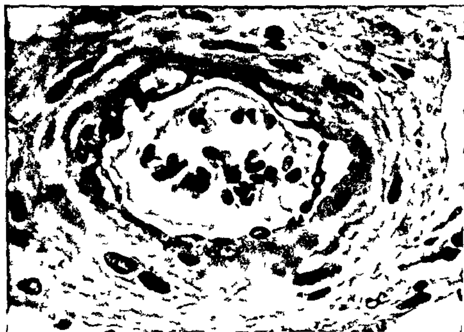


Fig 10 7 Fibrinoid necrosis of the wall of an arteriole involving half the vessel (lower and right) from a case of classic polyarteritis nodosa

leans toward the second view with the additional qualifications that all the forms of arteritis found in allergic diseases may occur as the result of other mechanisms as well and that all the described forms may occur in any of the clinical entities listed but with different frequencies

The unit lesion varies from a zone sometimes a crescent involving only a segment of necrosis in the wall of the vessel with little or no evidence of cellular reaction (Fig 10 7) to a marked inflammatory nodule or even a granuloma in the wall or around it (Fig 10 8) When the stimulus is a single event such as the giving

of a drug to which the patient is allergic the lesions tend to be in the same stage of development and to be of uniform size usually microscopic This corresponds to the type called hypersensitivity arteritis (Fig 10 9) When the stimulus lasts a long time or is re peated and in those protracted cases where the stimulus is un known the lesions are various increase in size and confluence leads to grossly visible nodules Standard descriptions of polyarteritis nodosa indicate that these nodules are around the artery at intervals like beads on a string but this pretty manifestation (Fig 10 10) is

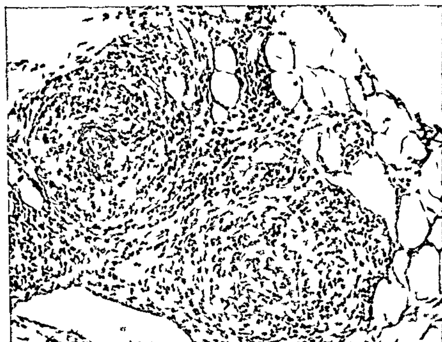


Fig 10 8 Necrotizing panarteritis from a case of classic polyarteritis nodosa

the exception More commonly the entire vessel is thickened al though not usually to the degree shown in Fig 10 11 In the well developed grossly visible nodule all layers of the vessel are involved the disease is not only a periarteritis as was originally assumed but a panarteritis The preferred name at this time is *polyarteritis nodosa*

For the sake of clarity the disease described by Kussmaul and Maier will here be referred to as *classic polyarteritis nodosa* and will imply both the symptom complexes which now often lead to clinical

Fig. 10.9 Necrotizing arteritis with hypersensitivity angiitis in the myocardium from a case of Butazolidin hypersensitivity

Fig. 10.10 Polyarteritis nodosa. Nodules are strung along the descending branch of the left coronary artery like beads on a string

diagnosis and the pathologic picture various as it is which is associated with these complexes It should be stressed at the outset that every histologic form described in any of the other arteritides may be found in classic polyarteritis nodosa indeed this fact is an important element in binding all these various lesions together in a group

Any vessel may be affected but certain ones are oftenest the site of lesions coronary renal adrenal hepatic and gallbladder and



Fig 10 11 Polyarteritis nodosa The descending branch of the left coronary artery is converted into a thick tortuous tube with a very narrow lumen This is an extreme case but diffuse thickening is commoner than Fig 10 10 shows

mesenteric arteries Whatever the nature of the early lesion—simple necrosis panarteritis or proliferating endarteritis (and all three may be present in the same case)—an ever present early change is damage to elastic tissue (Fig 10 12) Indeed it may be that some of the cases in which no known antigen can be blamed may depend upon autoimmune processes in which elastic tissue is the antoantigen Damage to elastic tissue and to muscle wall leads to formation of aneurysms along the course of a vessel (Fig 10 13) or to long fusiform aneurysmal thickenings and dilations (Fig 10 14) and the

Fig 10 12 Polyarteritis nodosa *elastic tissue (black) stain The elastic* tissue of a segment of the artery has been destroyed. In the necrotic portion there is a fine network of fibrin like threads



Fig 10 13 Polyarteritis nodosa kidney A microscopic aneurysm has formed which is filled with clotted blood

rupture of such an aneurysm may lead to sudden death The most common fatal hemorrhages are intrapericardial perirenal, and cerebral

Thrombosis may occlude vessels entirely leading to infarcts Infarcts in the heart muscle are uncommon in spite of the frequency of coronary artery lesions Although anemic infarcts of the liver are rare the most prominent cause aside from trauma is polyarteritis nodosa In the kidney many but slowly developing occlusions lead



Fig 10 14 Polyarteritis nodosa in a child long fusiform aneurysm of the axillary and bronchial artery which during life pulsated visibly Note abrupt ending of lesion at right

to numerous areas of depressed atrophy so called geographic kidney (Fig 10 15) Infarcts are seen in such unusual sites as testes hypophyses and thyroid

Various necrotizing lesions seen in cases of polyarteritis nodosa are not related to the arteritis but are probably the result of the same allergic process affecting other tissues Glomerulonephritis is common So is focal hepatic necrosis The frequent peripheral neuritis (foot drop wrist drop sensory changes) is probably not due to localization of arteritic changes in the nerves but to demyelinizing neuropathy Thrombocytopenia is not uncommon and granulocytopenia may be found

Some cases of polyarteritis nodosa show marked tissue and blood eosinophilia The highest recorded cases of eosinophilia are in this disease and sometimes this state is mistaken for eosinophilic leukemia All this while true has served to hide the fact that most cases of polyarteritis show no eosinophilia whatever



Fig 10 15 Polyarteritis nodosa geographic kidney due to atrophy of superficial parts of renal cortex

Special Forms of Arteritis When the arteritis involves special localizations or peculiar clinical courses or both it may receive special designation Of these the best known are temporal arteritis mammary arteritis (Mondor s disease) and salivary and lacrimal arteritis (Sjogren s disease) Localized benign forms are described

especially in the appendix and gallbladder Typical focal necrotizing arteritis may be seen after irradiation of malignant tumors Polyarteritis commonly accompanies malignant granulomas of the respiratory tract (Wegener s granuloma midline granuloma)

Rheumatic pneumonia and *Aschoff nodules* are anaphylactoid lesions They are adequately treated in standard texts of pathology

GRANULOMATOUS LESIONS

A granuloma is a nodular inflammatory reaction Lesions of microscopic and of gross size are both referred to as granulomas In the past granulomas were classified as nonspecific and specific and the latter were thought of as pathognomonic lesions the cause of which could be determined even without looking for the causative living agent The classic form of the specific granuloma was the *tubercle* It is recognized today that no such specificity exists The anatomic form of the tubercle is determined by the allergic state which exists and not by the causative organism a *living agent is not even necessary* and tuberculoid granulomas are found as reactions to chemical substances (e g beryllium) or to altered tissues (autoantigens e g in sympathetic ophthalmia)

We shall not discuss the foreign body and other nonspecific granulomas but shall confine our attention to (1) tuberculoid (2) sarcoid and (3) rheumatoid granulomas

Tuberculoid

The tuberculoid granuloma consists of a central focus of necrosis surrounded by histiocytes radially arranged and often in palisade fashion (Fig 10 16) The necrosis occurs in the inflammatory cells and remnants or shadows of these cells may still be seen For this reason also small granulomas may be seen (especially in the acute miliary forms) which as yet show no necrosis When the granuloma is caused by a living agent this agent may be found in the granuloma but it may require special staining methods to detect it Other features of the tuberculoid granuloma are variable There may be many giant cells or there may be none and these may or may not be of the Langhans type A zone of lymphocytes may be present on the outside and in the slowly developing or long standing lesions there may be connective tissue proliferation or calcification

In the days when tuberculosis was a common disease the clinical diagnosis of tuberculosis correlated closely with the anatomic diagnosis based on finding tuberculoid granulomas or tubercles as they were then called This is no longer true now that the incidence

of tuberculosis is low Among the conditions associated with tuberculoid granulomas are brucellosis histoplasmosis coccidioidomycosis glanders sporotrichosis cat scratch fever venereal lymphogranuloma trichinosis beryllosis and sympathetic ophthalmia Thus it is not safe to make an etiologic diagnosis when a tuberculoid granuloma is found unless complete bacteriologic confirmation is available



Fig 10 16 Tuberculoid granuloma from a case of brucellosis diagnosed bacteriologically There is caseation necrosis in center with palisaded histiocytes around it and lymphocytes in periphery

Sarcoid

The sarcoid granuloma occupies a peculiar place in this discussion The disseminated form is usually associated with a state opposite that of allergy—anergy—but exhibits some features such as dysproteinosis and plasmocytosis which somehow relate it to allergy and collagen diseases There are localized forms which have identical histology except that a foreign body can be detected Indeed it has been held that sarcoidosis may be a form of foreign body granulomatosis and that the foreign body may be at times local at other times dis

seminated that sometimes it may even be nonvirulent tubercle bacilli The lesions of beryllosis which previously were said some times to be tuberculoid are more often sarcoid granulomas

The characteristic sarcoid granuloma is made up of histiocytes which are irregularly arranged and which show no necrosis (rarely necrosis has been reported) Giant cells and lymphoid zones are ir regular components Asteroid inclusions are striking features usu ally within giant cells but they may be present in lipoid and other foreign body granulomas



Fig 10 17 Rheumatoid granuloma subcutaneous nodule at elbow Note fibrinoid necrosis of collagen in the center and palisaded histiocytes in periphery

Rheumatoid

The rheumatoid granulomas consist of a zone of fibrinoid necrosis surrounded by radially arranged histiocytes (Fig 10 17) The necrosis is in previously existing collagen and shadows of the original tissue can often be made out The zone of necrosis may stain by the special stains for fibrin hence the designation *fibrinoid* Giant cells and lymphocytic zone are rare

The subcutaneous nodules of both rheumatoid arthritis and rheu matic fever are of this nature the latter tending to be somewhat more vascular They may show grossly visible necrosis (Fig 10 18) The

of tuberculosis is low Among the conditions associated with tuberculoid granulomas are brucellosis histoplasmosis coccidioidomycosis glanders sporotrichosis cat scratch fever venereal lymphogranuloma trichinosis beryllosis and sympathetic ophthalmia Thus it is not safe to make an etiologic diagnosis when a tuberculoid granuloma is found unless complete bacteriologic confirmation is available



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COLLAGEN DISEASES

The next few yeirs will probably see a mirked broidening of the concept of the collagen diseases to include a large variety of hereditary and acquired conditions which have in common injury to connective tissues or ground substance and the deposit of abnormal substances in or on collagen fibers All these cannot be discussed here and consideration of even the best known group that associated with fi

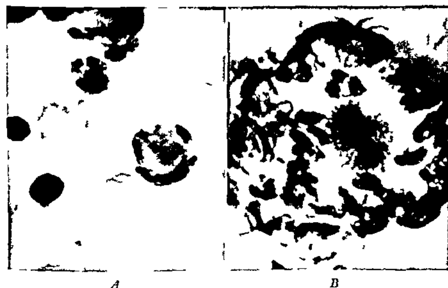


Fig 10 20 *A* LE cell A neutrophil leukocyte has phagocyted a mass of rather honogeneous nuclear material *B* An LE rosette A mass of nuclear material surrounded by a cluster of neutrophil leukocytes Both LE cells and rosettes tend to occur in the worst part of the slide (trauma is a factor) hence the poor detail in the other cells

brinoid degeneration can only touch the essentials The relevance of such a discussion in this book has been best expressed by Criep hypersensitivity is thus far the only clue to the etiology of these conditions

Hyperglobulinemia dysglobulinemia sometimes cryoglobulinemia plasmocytosis and arteritis are common findings in all of the collagen diseases In addition to the characteristic findings in each of the entities there are features of the others in many cases Polyarteritis nodosa which belongs in this group has been described above

Acute Disseminated Lupus Erythematosus Two types of change form the basis for the histopathology of this disease The first is damage to nuclei which results in the lupus erythematosus cell (LE cell) in preparations from peripheral blood or marrow (Fig 10 20) and in the hematoxylin bodies in the tissues (Fig 10 21) The second consists of the deposit of homogeneous hyaline eosinophilic

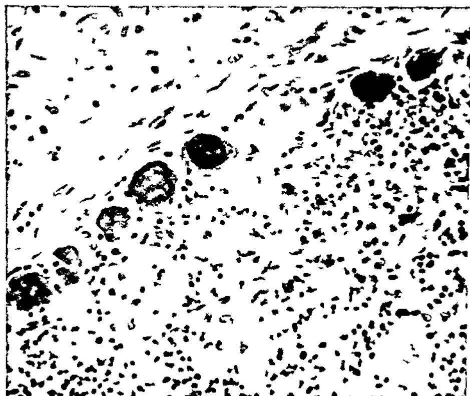


Fig 10 21 Acute disseminated lupus erythematosus lymph node showing hematoxylin bodies in a peripheral sinus These stain by the Feulgen method which indicates that they contain nuclear material (desoxyribo nucleic acid)

material between collagen fibers and beneath basement membranes The latter leads to the so-called wire loop glomeruli (Fig 10 22) and to the onion skin layering about the arterioles of the spleen (Fig 10 23) Fibrinoid necrosis may be present especially in arterioles (Fig 10 23)

Dermatomyositis The essential findings are infiltrations of inflammatory cells in the skin and in the muscle together with a tendency to necrotizing angiitis The degree in different cases is quite variable

Fig 10 22 Acute disseminated lupus erythematosus kidney showing thickening of glomerular loops by deposit of hyaline material beneath the epithelium— wire loop glomeruli

Fig 10 23 Acute disseminated lupus erythematosus spleen showing loosening and thickening of connective tissue fibers about a central arteriole— onion skin appearance Note the necrosis in the arteriolar wall

and the most severe cases may resemble a myositis due to a living agent (Fig 10 24) Some cases have accompanied malignant tumors have cleared up when the tumor was removed and have recurred when metastases appeared

Scleroderma The skin lesions of scleroderma are now known to be only one manifestation of what is undoubtedly a disseminated process The visceral lesions are not complications of a skin disease Indeed it is probable that visceral lesions may occur without skin lesions it may be that some of the obscure fibrosing diseases like

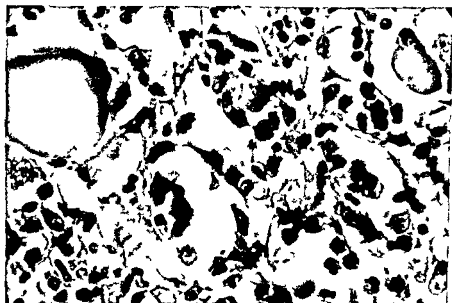


Fig 10 24 Dermatomyositis muscle showing unusually marked inflammatory infiltration between muscle fibers (*Material from a case of Dr J L Orbison*)

Hamman Rich fibrosis of the lungs or myocardial fibrosis without coronary artery disease may be of this nature

The skin lesion (Fig 10 25) consists of thickening increased number and hyalinization of collagen bundles in the dermis which gradually separates the skin appendages (sweat and sebaceous glands hair follicles) far apart from one another The fibers become more anisotropic than usual observation in polarized light is an excellent way of demonstrating the lesion Common sites of visceral involvement include the heart (Fig 10 26) lungs esophagus (Vinson Plummer syndrome) and kidneys Calcinosis (Thiebierge Weissenbach syndrome) may precede or follow the scleroderma The most com

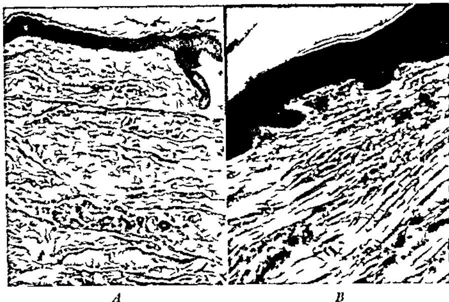


Fig 10 25 Scleroderma *A* Ordinary stain Notice thickening of collagen bundles thinning of the epidermis and the sweat glands and markedly increased distance of the sweat glands from the surface *B* Polarized light unstained preparation The increased anisotropicity demonstrates the increased thickness of the collagen bundles

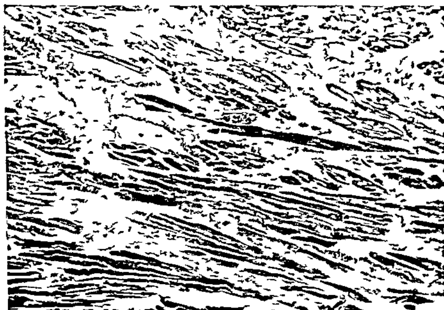


Fig 10 26 Scleroderma heart from a case of interstitial myocardial fibrosis without coronary artery disease

mon causes of calcinosis with normal serum calcium and phosphorus are scleroderma and dermatomyositis Other collagen diseases may also show this not uncommon finding Raynaud s manifestations are common in this whole group

Thrombotic Thrombocytopenic Purpura Allergic reactions are well known causes of thrombocytopenia Drugs are frequently the allergen and there are now methods for detecting the presence of

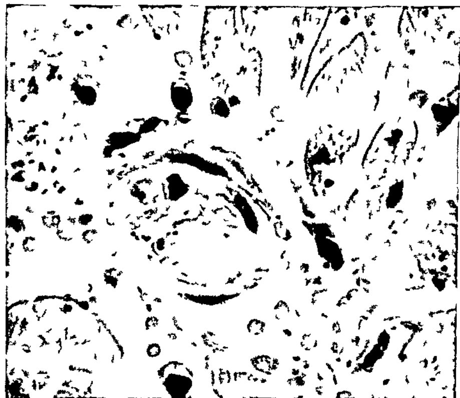


Fig 10 27 Thrombotic thrombocytopenic purpura myocardium Notice the endothelial cell over the surface of the hyaline lesion (*Material from a case of Dr J Adler*)

antibody in the serum of some subjects by adding drug and serum to platelet suspensions In the thrombotic type it was supposed that the platelets clumped to form platelet thrombi in the capillaries and in this way the platelets were filtered out of the circulation until the circulating platelets were too few to allow for blood clotting In many cases the numbers of such thrombi were too few to explain the low platelet counts it is probable that the lysis of platelets occurs here just

as it does in the usual thrombocytopenic purpura Furthermore the lesions in the capillaries do not always look like clumps of platelets

High power examination of the thrombotic lesions (Fig 10 27) often shows the hyaline necrotic mass to be covered by endothelium as though the essential lesions were *beneath* the endothelium and pushed the latter forward to occlude the lumen Orbison has recently reconstructed the lesions and shown them to be small aneurysms The name of the disease is therefore a misnomer

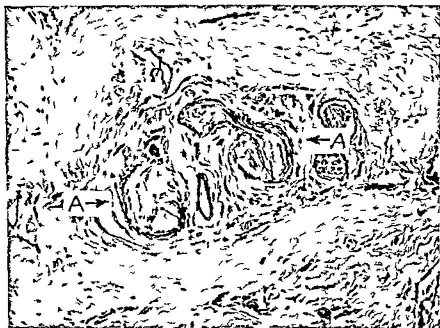


Fig 10 28 Amyloidosis gum biopsy At (*A*) the hyaline material in the well of arterioles stains intensely with Congo red

AMYLOIDOSIS

Amyloid is a homogeneous hyaline usually eosinophilic substance which gives certain specific reactions with dyes a marked affinity for Congo red (this reaction is used as a clinical test) metachromic reaction with several dyes especially crystal violet which stains amyloid red argyrophilia and above all a reaction with iodine which stains it deep mahogany brown It is this last reaction which resembling that with starch gave the substance its name Amyloidosis was formerly a not infrequent complication of purulent diseases such as chronic osteomyelitis or chronic empyema

and of chronic tuberculosis as these diseases became uncommon so did amyloidosis The amyloid was deposited in the viscera es pecially the liver kidneys spleen and adrenals This form is still seen although uncommonly without purulent disease A second form of amyloidosis affects principally the heart and the walls of small blood vessels No preexisting disease is found in many of these cases certainly no purulent disease or tuberculosis

There is an unfortunate tendency to call the second form *primary* amyloidosis and the first *secondary* In my experience which includes over 80 cases (60 of them furnished by the Armed Forces Institute of Pathology) the commonest type is a mixed type It is better to use the terms *parenchymatous* and *vascular* for the two types

Because deposits of amyloid in the liver often make this organ very brittle there is danger of severe hemorrhage following puncture biopsy of the liver A much safer source for tissue in suspected cases is a gingival biopsy (Fig 10 28) The sections should be stained by one or more of the special stains for amyloid preferably Congo Red

Allergy and collagen diseases are common in the histories of pa tients with amyloidosis It has followed long standing use of vac cines It is common in multiple myeloma and even without this is commonly associated with plasmocytosis and hyperglobulinemia

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PART TWO

TESTS PROCEDURES AND TECHNICS FOR DIAGNOSIS OF ALLERGIC CONDITIONS

Louis Sternberg

11

HISTORY TAKING IN ALLERGY PRACTICE

A detailed and well organized history is of inestimable value when seeing the allergic patient on his first visit A full hour should be given for the initial interview in a period when one is not rushed or interrupted by phone calls or the presence of other patients in the waiting room At such a time both the physician and the patient can be at ease and not under any undue stress Questions and answers can then be discussed properly A complete history will help not only in making the initial diagnosis but throughout the period that the patient is under observation and treatment Minor revelations at this time may turn out to be important later on as the patient is observed A careful and detailed history will also help to create good will and engender confidence in the patient without which little can be achieved and the good doctor patient relationship developed will help the patient to impart on subsequent visits information he could not divulge in the beginning

Since allergy patients frequently present themselves at a time when physical examination does not reveal evidence of disease the diagnosis will depend a good deal on the history All physicians have seen patients with asthma who were perfectly well in the office although the night before they had suffered a paroxysm that required epinephrine for relief

The history that patients volunteer should be listened to carefully They often tell of certain foods and inhalants that bring on their attacks of asthma or rhinitis and when their confidence has

been gained they may also admit that these attacks sometimes follow an argument at home or in the office *A reliable history is more important than a positive skin test* for the latter is of value only if it can be correlated with the history of the patient

Skin tests should never be made before the history is completed since the testing material may need to be diluted a good deal or some tests eliminated when the patient says that he is highly sensitive to a particular food or inhalant The history will also be a guide to the number and kind of skin tests to be performed Hence both negative and positive skin reactions will be important only when the history confirms their value

The physician should always endeavor to deal with the allergic patient patiently probe gently and remember that these patients are highly sensitive individuals Many of them have been ill for a long period and need sympathy and understanding in addition to the relief of their symptoms If the patient is a child it is best to make him wait outside the consultation room while taking the history from the parents The physician can then impress the parents with the fact that it is advisable to discuss the illness of the child behind closed doors both at home and in the physician s office The reason for this is that we are dealing with a chronic disease the child may be ill for a long time and therefore should not be made to feel apprehensive or self-conscious or allowed to develop a feeling that he is different from his playmates The mother is also instructed not to ask the child too often how he feels or nag him constantly about what he can or cannot do The intelligent mother can tell whether or not her child is well without asking many questions She should be interested in the welfare of her child without showing undue anxiety If the patient is a teen ager the doctor should arrange a session without the presence of the parents All concerned should be assured that the interviews will be confidential and that frank discussions will result in a better understanding of the patient s problems thereby making the treatment more effective

For convenience history taking may be divided into the categories shown in the appended questionnaire used by the author (Fig 11 1) This is an outline of the most common questions posed to the patient Not all allergic patients have to be questioned in detail The hay fever patient needs but a few questions the asthmatic on the other hand requires a fuller inquiry Although the approach may be standard for each allergic disease entity the questioning must be individualized Let us now turn to the major questions covered by a good history

Referred by

Name Age Date

Address S M W Occupation

Chief Complaint

Family History of Allergy

Relative	Age	Age at onset
Father		
Mother		
Sibs		

Present Illness

1 Age at first attack
2 Perennial or seasonal?
3 Followed infection? Change of food? Location? Etc
4 Course
5 Place of first attack
6 Attacks influenced by weather changes dampness cold smoke dust odors drugs foods plants excitement exertion
7 Symptoms
8 Location Day Night
9 Relief obtained by
10 Expectoration

Past History

1 Nose and throat conditions Sinuses
2 G I disorders (food idiosyncrasies)
3 Respiratory infections (Flu In Bronchitis) Susceptibility to colds
4 Other allergic conditions (Eczema H F Hives)
5 Serum injections
6 Operations

Personal History

1 Weight present past General health Menses
2 Business contact Home contacts
3 Animal contacts
4 Bedding Sachets Insecticides
5 *Constipation Diarrhea Alcohol Tobacco Drugs*

Previous Treatment and Results

Summary

Fig 11 1 Outline of history for allergic patients

CHIEF COMPLAINT

What is your problem? is the first important inquiry to the patient When asked that question some patients reply with a diagnosis instead of listing their complaints The physician should rarely interrupt the story that the patient is eager to relate However guidance is sometimes necessary or the questioner is swamped with irrelevant material which reveals the personality of the patient but does not disclose enough about the patient s illness These loquacious patients should be told politely that what the physician wants to know is whether they cough wheeze sneeze suffer from skin eruptions or have other complaints which need attention When the chief complaints are satisfactorily stated it is then advisable to allow the patient to do all the talking and if the allergist then listens to the story in detail without interruption he can learn a good deal about the patient He often gets insight as to the kind of person he is dealing with his emotional background his family relationships his marital status and his reliability

It is impossible to give in detail all the questions that the physician should ask during the initial and subsequent visits These will depend on his experience and training and the problems that present themselves in each case The questions will also depend on the patient s answers which may in turn initiate further questioning

PRESENT ILLNESS

Begin with the present age of the patient and the age of onset of the illness At what period of the year did the symptoms begin? Was infantile eczema the precursor of the present symptoms? What precipitated the first attack and where? How frequently did attacks appear at first? Subsequently? In children it is likely that a food was involved in the beginning then as time went on inhalants and later infection became the causative factors Do these attacks occur in paroxysms or are they more or less continuous? If the seizures are intermittent some extraneous contactant or some particular dust or a food eaten occasionally may be the factor If on the other hand the attacks are continuous and do not vary during environmental changes some respiratory infection has to be considered Are the attacks seasonal or perennial? In the summer pollen or a mold is a likely cause In the winter infection has to be considered If nonseasonal inhalants foods and infection may be present in combination and each possibility will have to be evaluated Did the original paroxysm follow an upper respiratory infection pneumonia pertus

sis scarlet fever or measles? Does the patient live in the city or country? Does he live near a factory where he is exposed to certain allergenic or irritant waste products? Is his home dry and inhabited all year round? A summer house that is left neglected during the winter months can become a breeding spot for various molds and the patient may be sensitive to their spores He will then sneeze wheeze or cough every time he enters that house

In the adult it is important to know the occupation since there may be exposure to allergenic inhalants and dusts encountered in certain industries Bakers furriers painters upholsterers and chemists among others come in close contact with allergenic dusts and other irritants in their daily work Irritating fumes gases and even perfumes are other factors that can precipitate allergic attacks

Some patients are sensitive to drugs and should be questioned about such possibilities The most common drug allergens are aspirin penicillin quinine and the sulfonamides

Food sensitivities as already mentioned are more apt to occur in childhood Sometimes a patient will develop a dislike for a food to which he is sensitive Adults usually lose their food sensitivities although they may carry the antibodies to these foods in their blood and tissues for many years They may therefore show a positive skin reaction to a particular food they were clinically sensitive to years before but are able to tolerate now Sensitivity to a food should not be disregarded but should be investigated carefully Many times suspicion is not warranted nevertheless occasionally it points in the right direction Some patients are so highly sensitive to a food that even its odor or minimal contact with it will produce an allergic reaction The odor of fish or coffee can cause asthma or vasomotor rhinitis in those who are so hypersensitive Some patients suffer severe cramps nausea or vomiting when they partake of the smallest amount of the food to which they are highly sensitive In fact the infinitesimal amount that is introduced in a skin test will sometimes produce a constitutional reaction in these patients It is therefore important to ask about these sensitivities and to be cautious when testing with the antigens concerned Known sensitivities should not be minimized by the novice in allergy

PAST HISTORY

Eczema in infancy as previously mentioned is a frequent forerunner of asthma in later life Cyclic vomiting or colic in infancy may have been manifestations of allergy One must also be aware that a history of frequent attacks of bronchitis or pneumonia

in childhood may indicate attacks of asthma not properly diagnosed The same may be true of a past history of sinus trouble which in our experience usually turns out to have been allergic rhinitis and only rarely sinus infection

Has the patient been operated on for nasal polyps? A positive answer is suggestive of allergy

Has the patient any other allergies besides the one that is his main complaint? Does he feel better when away from his home or place of business? The answers to these questions may establish the allergic background of the patient and indicate contact with specific allergens

Concerning the possible role of infection in asthma or allergic rhinitis it is important to know whether these are aggravated by repeated upper respiratory infection or by injected vaccines

A history of a reaction to horse serum is very important and puts the physician on guard in the event of future need for a similar injection The same holds true in a history of hypersensitivity to drugs as mentioned before It is also important to remember that gastrointestinal complaints diagnosed as gallbladder disease appendicitis or renal colic may have been manifestations of hypersensitivity When these complaints are associated with asthma hay fever allergic eczema or vasomotor rhinitis they are more readily diagnosed correctly Furthermore when these gastrointestinal complaints exist in the absence of overt allergic disease but in the presence of a familial history of allergy allergy as a cause should be ruled out before any other diagnosis is made

PERSONAL HISTORY

The general health of the patient present and past should be gone into It is important to inquire about menstrual cycles in female adults The relation of asthma attacks to the cycle of menstruation to the menopause and to pregnancy are important considerations Asthma allergic rhinitis and allergic eczema are sometimes aggravated during or just before the menstrual period Some patients find that their hay fever or asthma is completely relieved during pregnancy The menopause occasionally diminishes or relieves various allergies in some women in others these allergies are made worse Puberty in the male is occasionally followed by a lessening or complete disappearance of allergic attacks In the female these attacks may first begin at that period

Queries should be made as to the presence of pets such as cats

dogs or rabbits in the environment Does the patient use insecticides in his home or garden? What are the smoking habits? What kinds of cosmetics are used? All such data are important and may have some bearing on the patient s illness

Once the allergic pattern of symptoms has been established an asthmatic patient may develop an attack following a heavy meal while walking against a wind during changes in atmospheric pressure after exertion or a hearty laugh while straining at stool or during a quarrel or any excitement

Then there are patients in whom stress or strain initiates or aggravates whatever form of allergic symptoms they have been suffering from The author has seen a paroxysm start in a ten year old patient with pollen asthma when she felt neglected watching her mother kissing and hugging her year-old niece Hence relations at home between husband and wife and between the parents and their allergic child as well as between the child and his siblings should be made an integral part of a complete history

FAMILY HISTORY

This is important not only for statistical purposes but also for clues to the diagnosis It is now well recognized that the tendency for allergic diseases are often transmitted from one generation to the next Occasionally a generation is skipped and the next one continues the cycle When another member of the family is suffering from an allergic manifestation it is reasonable to assume that the complaint of the patient also belongs in that domain About 50 per cent of patients give a positive history of allergy in their family

PREVIOUS TREATMENT AND RESULT

What type of treatment was previously administered? What steps were not undertaken? What diagnostic or therapeutic procedure was omitted? Which drugs gave relief? Does the patient use drops or nasal sprays to shrink the swollen mucosal membrane and how frequently? Was the patient ever given skin tests? With what results? Was any operation performed on the nose and throat and if so what were the results? Many patients have had X ray studies made of the chest and sinuses before coming for consultation These may be important to see if they were made recently or to compare with any new studies indicated Answers to these questions will help a great deal in the management of the patient

SUMMARY OF THE HISTORY

This should include the most important points gathered so that they can be referred to readily without reviewing the detailed history

The above method of history taking is an outline only One can add or delete questions depending on the individual case The physician should not bombard each patient with stereotyped questions The inquiry should be friendly reasonable and intelligent with the realization that each question has its significance and purpose

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DIAGNOSTIC PROCEDURES IN ALLERGY

This discussion concerns itself with the diagnostic procedures commonly employed in the specific diagnosis of atopic allergic diseases a group of illnesses based primarily on a hereditary predisposition Included among the most important manifestations of atopic allergy are asthma hay fever perennial allergic rhinitis atopic dermatitis urticaria angioedema and migraine No single immunologic mechanism mediates all these conditions but when an antibody is demonstrable in the patient s blood or tissues it is usually the atopic reagin or skin sensitizing antibody This antibody is not pathognomonic of atopic allergy and may occur in normal individuals following treatment or contact with unusual antigens such as animal serums intestinal parasites and antibiotics Moreover the absence of reagins does not exclude a diagnosis of atopic allergy which may occur in the predisposed individual without positive skin reactions and even without the participation of an immunologic mechanism

In the diagnosis of atopic allergic illnesses no procedure exceeds in importance the procurement of a detailed and careful history This and a complete physical examination will usually not only establish the clinical diagnosis of atopic allergy but in most instances will determine the need for other diagnostic procedures and also their scope In many allergic conditions such as chronic urticaria angioedema drug sensitivity some types of migraine and gastrointestinal disturbances skin tests contribute little information and

other diagnostic measures are indicated The procedures most frequently employed in the search for specific excitants which cause atopic allergy are (1) the skin test (2) ophthalmic tests (3) nasal tests (4) environmental tests and (5) dietary studies

THE SKIN TEST

There are many varieties of this specific method of diagnosis which seeks to determine not only whether the patient is allergic but also the specific allergenic offenders responsible for his symptoms The skin test may be regarded as a method of detecting the presence of atopic reagins which are found not only in the circulation but also in the skin mucous membranes and other tissues The union of the reagin in the skin with its related antigen (allergen) applied in the skin test causes the release of histamine or a histamine like substance by the tissues and results in an urticarial reaction This usually consists of a wheal of variable size and shape surrounded by erythema and frequently accompanied by pruritus

The technic most commonly employed in general practice is the *scratch test* A series of superficial scratches or abrasions about ⅛ in long are made on the cleansed skin of the arm forearm or back Over these scratches which should not be deep enough to cause bleeding allergenic materials are gently applied For the worker who tests only occasionally the use of dry allergenic powders dissolved in alkaline solution applied on the scratch is desirable because of the stability of this type of test material Others prefer to use extracts prepared with glycerin or other solvents and preservatives After fifteen or twenty minutes the allergens are removed from the skin and the reactions at the test sites are read and interpreted on the basis of comparison with control tests which have been made with diluents devoid of allergenic principle

For the well trained allergist and the research worker the *intracutaneous technic* is the method of choice It involves the introduction into the skin of about 0 01 ml of a sterile allergenic extract used first in high dilution and later in more concentrated form The lateral surface of the arm is preferable for this technic The reactions resulting from the intracutaneous technic are generally larger than those obtained with the scratch technic and the standards of recording and interpreting vary with each procedure (Fig 12 1) When used injudiciously in highly sensitive patients the intracutaneous test may cause severe constitutional reactions consisting of urticaria asthma allergic rhinitis shock and in rare instances even death within a matter of minutes The immediate application of a tourniquet above

the test sites if they have been performed on the extremity and the early hypodermic administration of epinephrine above the tourniquet will usually control the reaction

In determining the nature and number of tests to be performed the clinician is guided by the history of the patient the severity of his symptoms his age and the nature and concentration of the allergens employed When the history points to an unusually severe clinical sensitivity to a known allergen or group of allergens skin testing with such offenders should be approached with caution and if possible postponed until the clinician has had the opportunity of studying the patient s allergic status more carefully

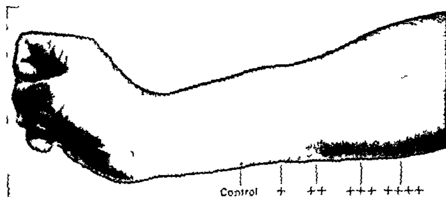


Fig 12 1 Skin testing showing graded reactions from slight (one plus) to marked (four plus) reactions (*Courtesy of Medigraphics Inc New York*)

In interpreting positive reactions there are many factors to be considered in addition to the specific histamine releasing effect of the antigen reagin reaction The size of the reaction is by no means an indication of its clinical significance Although reactions are considered positive if they are larger than the controls their reliability diminishes as the size of the control increases

The introduction of too large an amount of test material into the skin (more than 0 01 ml) and the unskilled performance of the tests are common causes of nonspecific (traumatic) positive reactions Other major causes of nonspecific positive reactions include the use of extracts that are too irritating and the crowding of tests too close to each other causing reactions that would ordinarily be negative to light up because of their proximity to strong positive reactions For these reasons all positive reactions should be confirmed by repetition preferably at a subsequent date

Positive reactions even when specific and well controlled are not absolute indications of an existing clinical sensitivity They may be residuums of past clinical sensitivities or the forerunners of future ones

Negative reactions need evaluation as much as positive ones Theoretically negative reactions should indicate the absence of reagins for the allergen tested but other considerations such as the use of inadequate weak or deteriorated extracts can account for them In food sensitivity the patient may be sensitive to a derivative of the allergen and not to the natural substance which is used for testing Even more significant is the misguided search for reaginic antibodies by skin tests in those allergic illnesses already mentioned in which reagin mechanisms play no role

Delayed reactions vary in mechanism and significance and are unreliable for diagnostic purposes

In seeking to evaluate the comparative merits and disadvantages of the scratch and intracutaneous technics there are many points to be considered The intracutaneous technic is conceded to have greater diagnostic potentialities On the other hand it is dangerous in inexperienced hands The expert has learned to prevent constitutional reactions but such dangers are still formidable for the novice who would be well advised to restrict himself to the use of the scratch technic Lest the unwary be misled by irresponsible assurances that intracutaneous tests with an allergen are safe if a preliminary scratch test with the same allergen is negative it should be pointed out that even such a precaution is not foolproof when the testing materials employed for the scratch tests are not dependable

No technic is better than the technician who uses it The diagnostic value of the technics will depend more on the clinician s ability to interpret his results correctly than on the elicitation of positive reactions Both the scratch and intracutaneous technics will prove valuable to any worker who will take the time and effort to study and understand the procedure and materials he is using

When skin testing of the patient is impractical or impossible because of cutaneous disease severe illness or other complications the *indirect (passive transfer) method* is indicated By introducing small amounts of the patient s serum into cutaneous sites on a normal substitute sensitized areas are created which may be tested intracutaneously after a few days for sensitivity Each test is controlled by a similar test on the neighboring unsensitized skin An excess of reaction at the sensitized site over the control represents a positive reaction This excellent control (which has no equivalent in direct testing) is one of the greatest assets of the passive transfer

technic However the indirect method of testing is an involved procedure which requires considerable experience for its effective performance

Tests with pooled allergens in the form of group tests are neither time saving nor trustworthy One irritating extract in the group may falsely *implicate all its component allergens A positive reaction neces* sitates separate tests with all members in the group Group testing merely multiplies the pitfalls which are encountered in testing with individual allergens

PATCH TESTS

Patch tests are limited to the diagnosis of contact type dermatitis and are discussed in detail in Chapter 32

OPHTHALMIC TESTS

A stronger allergenic extract is needed to produce a positive ophthalmic reaction than to induce a positive intracutaneous re action However the conjunctival test is more sensitive than a scratch test with the same material

The ophthalmic test is most valuable in interpreting the clinical importance of some positive skin reactions For instance a positive ophthalmic reaction to horse serum is an absolute contraindication to the systemic administration of horse serum whereas a positive *intracutaneous reaction to this allergen carries no such prohibitive* implication

NASAL TESTS

Insufflation tests with pollens molds dusts and similar inhalant allergens are not too helpful because of the lack of good controls It is as difficult to differentiate between specific and irritative re actions in the mucous membranes as it is to make a similar dif ferentiation in reactions in the skin

ENVIRONMENTAL TESTS

Such investigations are of value when there are many etiologic possibilities to be ruled out particularly in cases of respiratory al lergy The sudden dramatic improvement of a patient when placed in an allergen free room or in a similarly controlled environment suggests the importance of inhalant allergens as the causative factor in his case However the value of the test is nullified by initiating

radical changes in the therapeutic regime simultaneously with the environmental change

DIETARY STUDIES

A study of the patient s carefully kept records of his food and drug intake and their chronologic relationship to allergic symptoms may prove more helpful than skin tests in the diagnosis of some allergic conditions One may resort to stereotyped systems of food elimination and trial feedings as for instance the Rowe diets However the more experienced investigator often prefers to vary his regime according to the patient s symptoms and needs The gradual elimination of suspected allergens from the patient s normal diet is more likely to be successful in the long run than is the use of radical or starvation regimes If these stern measures do not meet with immediate and striking success the patient is likely to become discouraged by the severity of the regime and to seek other methods of obtaining relief (See also Chap 42 Food Allergy)

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IMPORTANT ALLERGENS EASILY OVERLOOKED

It is the purpose of this chapter to record a group of allergenic agents which although very important etiologically in certain allergic disorders are easily overlooked It should be stressed that the allergenic agents to be listed can in most instances be causative agents for many diverse allergic states

EPIDERMAL ALLERGENS ANIMAL EMANATIONS AND OTHER ODD ALLERGENS

Animal danders may be inhaled through direct contact with the living animal or indirectly from animal products Animal products such as feathers from the chicken goose or duck or hair from the horse or rabbit are important air borne allergenic agents easily overlooked Hair from many animals—rabbit goat hog fowl—as used in manufactured articles such as hair pillows and mattresses may provoke diverse allergic disorders It should be kept in mind that rabbit epithelium may lurk in a felt hat and velvets and plushes from the Angora goat may be used in the manufacture of automobile and railroad car seats Camel hair often mixed with wool may be used in the manufacture of blankets and wool may be used in outer and undergarments and in carpets and rugs Hair or bristle from the hog is also used in tooth hair and shaving brushes The relationship of certain animals to furs marketed under trade names is apt

to be misleading in searching for a diagnostic basis Not to be over looked is the fact that epidermal substances, such as dandruff from human beings may rarely be allergenic

Emanations and odors from certain animals may also produce symptoms of various allergic states *even though the individual af* fected may not have been in direct contact with the animal Like wise air borne allergens may be transmitted indirectly to hyper sensitive individuals by means of garments or other possessions of a person who actually contacted the animal

Direct contact with the mouse rat dog or cat can occur in the home For hunters contact with deer and for laboratory workers contact with the guinea pig or rabbit should be considered Contact with birds including pigeons canaries parrots or sparrows may also be responsible for allergic manifestations

Odors and Fumes

The allergic effects of inhaling odors of fresh vegetables such as peas beans lentils and garlic are frequently experienced by sus ceptible individuals The aroma of coffee the smell of gasoline fumes and fresh paint odors as well as tobacco smoke in nonsmokers have been found to be provocative factors in some cases although not necessarily on an allergic basis

Insects

Insect sensitivity is restricted to three orders (1) the Lepidoptera or moths and butterflies (2) the Trichoptera or caddis flies [1] and (3) the Ephemerida or May flies In the moths and butterflies and the caddis flies the scales or hairs are produced in flight as a dust Par lato [2] did most of the early work on this phase of allergy He showed that moths and butterflies by virtue of their emanations can act as *allergenic agents in areas where these insects are abundant Skin* tests with extracts of hairs and scales of these insects were found posi tive by both direct and passive transfer methods

Insect Bites

Bees Wasps and Mosquitoes Fatal reactions can result from bites or stings of these insects Knowledge of the bee allergens causing al lergic disorders was greatly advanced by Benson [3] who proved the reaction to be due to the bee protein and not to the venom In the mosquito reactions edema and inflammation occur in a de layed manner twenty four to forty eight hours after the bite Here too it is the protein that causes the reaction (See Chap 45 for further details on insect sensitivity)

Fleas, Lice and Bedbugs. Studies of allergy to flea bites were made by Boycott[4] who demonstrated that the first bite fails to produce a reaction but subsequent bites do. Various species of fleas cause different reactions. Asthma resulting from bedbugs was reported by Sternberg;[5] other forms of sensitivity to their bite, by Parsons.[6] Swelling of the arm, choking, and general collapse were immediate reactions. The shock symptoms had been wrongly attributed to coronary occlusion. A local reaction in addition to a noticeable drop in blood pressure followed a subsequent bite.

Parasites

Among the parasites, flatworms (Platyhelminthes), roundworms (Nematoda), and trichinae (Trichinidae) are known to act as allergens and may cause manifestations resulting in bronchial asthma and other atopic states. Positive cutaneous reactions with extracts of these parasites have been reported. The mechanism of immediate cutaneous reactions resulting from these tests has been demonstrated by Rackemann and Stevens and by Brunner[8] to be mediated by reagins.

Testing with the *Ascaris* allergen will detect *Ascaris lumbricoides* as an intestinal infestation and may also reveal the presence of other members of the roundworm family. It bears no relation, however, to tapeworm sensitivity. It has been reported that laboratory workers in contact with these worms, if sensitive to them, have reacted with severe urticaria and asthma.

Patients having an echinococcus cyst of the liver have been known to suffer anaphylactic shock when the operating surgeon accidentally ruptured the cyst, releasing overwhelming allergens.

VEGETABLE GUMS (NONFOOD SOURCES)

Of the many vegetable gums, karaya, gum arabic (acacia), and tragacanth are the most frequent sensitizing agents.

The term *gums* is loosely applied to the resinous exudates which contain a carbohydrate that is capable of mixing with water—mucilaginous mixtures. The chief sources of sensitization are karaya in hair waving lotions and acacia in the offset sprays used in the printing trades. Although these allergens may enter the system by ingestion (discussed later), injection, or surface contact, *inhalation* is the most common route, and respiratory symptoms predominate.

Any of the three gums mentioned above may be contained in the list of articles in Table 7.[9] Patients sensitized to these agents manifest an allergic disorder after inhalation of or when in contact with

these substances The gum allergens very often overlooked are frequently substituted for one another Their presence is no doubt even more widespread than indicated in Table 7

TABLE 7 NONFOOD SOURCES OF GUM ALLERGENS

Adhesive pastes	*Luster for textiles*
Artificial flowers	Match manufacturing
Body and drier lithographing inks	*Metal polish manufacturing*
Cement	Mucilages
Cigar manufacturing	Paints
Coating for special thread	*Porcelain and pottery manufacturing*
Denture adhesive powders (Dent A Firm Stix)	Printing ink manufacturing
Emulsions (mineral oil cod liver oil turpentine almond and flavor)	*Process engraving*
Fireworks	*Shoe polishes*
Furniture polishes	Sizing for paper and textiles
Glues	Sprays (offset in printing trade)
Insecticides	*Starch (special)*
Laxatives (Imb coll Mucara Squibb's petroleum and agar)	Suppositories
Linoleum and oil cloth	*Toothpaste (Listerine and Lactora)*
Lotions (cosmetic for hand care hair waving etc)	Textile printing
	Vaginal jellies
	Varnishes
	Water colors *(transparent)*

CHEMICALS

It is not always easy to prove the etiologic relationship between certain chemical substances and the onset of various allergic disorders since skin testing direct or indirect is unreliable in these instances That certain chemical substances definitely cause symptoms is deduced in many indirect ways (1) by a history of exposure (2) by the fact that away from such contacts the patient is free from symptoms and (3) by provocative tests to prove the etiologic relationship of these chemicals to the allergic disorder

Paraphenylenediamine a fur and hair dye[10] and the diazo dye para red (paranitraniline red) first described by Oliver in 1926 as causing rotogravure ink dermatitis[11] must be listed among the chemical allergens Also to be included among the chemical sensitizers are paramidophenol arsenic aniline dyes and chinodiamine (which results from the addition of a weak solution of hydrogen peroxide to paraphenylenediamine) inhaled by workers in the form of dust[1]

The number of chemicals causing skin conditions is numerous Lead mercury nickel and other metals are possible agents to be

considered as causes of dermatitis Persons exposed to lead dust also may suffer asthmatic attacks when exposed to lead fumes

Cosmetic and other toilet preparations contain many chemical substances that may provoke allergic manifestations These include resorcinol linseed oil bichloride of mercury quinine sulfate in hair tonics bleaches and ointments tetrabromofluorescein and difluorescein in lipsticks and rouges [13] toluene sulfonamide formaldehyde in nail polish acrylic nails and acrylic dentures [14] Soaps dentrifices depilatories and orris root in face powders are also important offenders

Arsenic and Its Compounds

The allergic nature of the reaction to arsenic has been well established by various investigators Nathan and Grundmann [15] found by experimental studies that this allergic reaction induced by intradermal deposition was limited to the salvarsans the arsenic compounds of the aromatic series formerly used in the treatment of syphilis

Arsenic as a potential allergen may be taken into the system in a disguised form It may be ingested in milk eggs fish or other animal foods when this chemical has been employed in the feed of the animals Fruits and vegetables grown in soil in which arsenic has been used as an insecticide agent may carry this antigen It is also contained in paint wall paper and colored wood stains [16]

The author [17] has reported a case of hypersensitivity to arsenic resulting from the application of a well known hair tonic and dandruff remover Intolerance manifested itself as a marked generalized dermatitis Arsenic was shown by means of patch and passive transfer tests to be the etiologic factor

Other Drugs Additional drugs which must be viewed as important offenders are aspirin quinine epinephrine aminophylline Pontocaine Argyrol quinidine Sedormid the barbiturates penicillin streptomycin insulin liver extract phenolphthalein and many others Sedormid [18] and quinidine [19] [0] sensitivities may cause purpura as was recently demonstrated by positive passive transfer tests (see Chap 46)

FOODS

Common Foods

It is generally recognized that common foods such as wheat eggs and milk cause manifestations in predisposed allergic individuals

What may not always be realized however is the fact that these foods may be hidden ingredients of other food products

Wheat The most common of these excitants is wheat one of the most widely used cereal grains from which flour of different degrees of fineness is produced It should be noted that other flours including rye whole wheat buckwheat graham and gluten usually contain wheat flour Wheat flour not only is the chief ingredient of breads crackers cakes and the like but is employed in the preparation of many foods in which its presence is unsuspected Included among these are macaroni spaghetti gravies cream sauce soups various infant foods and breakfast cereals Wheat is also used extensively in coffee substitutes such as Postum and in some varieties of sausage Persons who are sensitive to wheat often are sensitive to other cereal grains—rice barley corn oats and rye

Eggs Like wheat eggs are contained in many prepared foods and provoke reactions in patients allergic to them who were unaware of their presence in the ingested product These foods include custards and various other puddings ice creams and ices some candies almost all cakes including macaroons griddle cakes and muffins some cake and pancake flours waffles egg noodles mayonnaise some salad dressings and Ovaltine The white of egg that is often brushed on breads rolls and pretzels to provide a glazed appearance may in some instances be the solution of an allergic diagnostic problem

Ratner and Untracht [1] found the incidence of egg allergy to be approximately 0 5 per cent in the general population and 5 per cent in allergic subjects They studied sensitivity in children with special reference to the increasing use of viral and rickettsial vaccines prepared from egg [2] It is interesting to note in their observations that *although serious reactions could result in patients sensitive to egg* the hazard of sensitization from repeated injections of vaccine prepared from egg seemed negligible

Milk Milk is also found in many foods in which its presence may not be suspected It is included in many types of white bread cakes of various kinds custards candies ice creams cream soups and sauces noodles macaroni spaghetti and many other foods including some infant foods

Milk allergy produces respiratory gastrointestinal cutaneous or other expressions of allergy It contains four distinct proteins casein lactalbumin lactoglobulin and an alcohol soluble protein [3] any one of which may be the sensitizing substance

Sensitization may also depend on whether the milk is ingested in its raw state or has been evaporated heated or boiled Ratner and

Gruehl [4] in a study to ascertain why milk modified by heat can often be tolerated by persons who are sensitive to it in its raw or pasteurized state regard the loss of antigenic properties in heated milk as probably due to the coagulation of the whey proteins In addition the process of heating by promoting digestion diminishes the likelihood of absorption of native proteins through the intestinal wall

Fruits With fruits as with milk a greater tolerance is usually obtained when they are heated than when otherwise ingested This was demonstrated by Tuft and Blumstein [5]

Fries and Glazer [6] found that the dehydrated banana was not anaphylactogenic in the guinea pig even though raw banana produced anaphylaxis Therefore they suggest that dehydrated banana may have a definite place in the hypoallergenic diet

Food Contaminants

Randolph [7] believes that the chemical contaminants in common foods are capable of causing allergic reactions in certain patients who are intolerant to these exposures He indicates that the technologic chemical contamination of foods by petro sulfo chloro and other halogenated compounds produces sensitization He cites examples of patients who were clinically sensitive to peaches but who were able to tolerate unsprayed unsulfured unfumigated and wormy peaches Peaches dusted with sulfur and those treated with chlorinated hydrocarbon oil mixture as a fungicidal agent precipitated acute allergic reactions The same holds true for tolerance to the ingestion of dates and figs these fruits fumigated with methyl bromide also resulted in the production of a severe reaction in certain allergic individuals

Contaminated human and cow s milk can cause allergic symptoms Pinto [8] noted sulfanilamide and acetylsulfanilamide in human milk after it was ingested by the mother Glazer [9] reported penicillin in human milk and cow s milk may contain traces of penicillin used in treatment of the animal for acute mastitis Cottonseed meal and linseed meal may also be present in cow s milk Luisada [30] observed favism in infants the source of the bean allergen being traced to the mother s or to goat s milk Other substances both chemicals and foods which had been included in the diet of cows or lactating mothers have caused allergic reactions [31] [3] It is therefore essential to realize that as in these instances an allergic response may be attributable not to the milk to which these infants and others are tolerant but to the contaminants which they contained

Figley and Rawling [33] and Coulson and his coworkers [34] have

shown that green coffee can become contaminated with castor bean dust when packed in burlap coffee bags which previously contained castor beans Their patients were sensitive to both green coffee and castor bean but were able to drink uncontaminated roasted coffee without symptoms the labile allergenic fraction having been re moved by the roasting

Sheldon and Yorke[3] reported a case of eczema associated with anorexia and mental depression and showed that the patient s symp toms were directly due to the consumption of bread or flour which contained either nitrogen trichloride (agene) or chlorine dioxide

Randolph[36] stressing the importance of starch sensitivity claimed that provocative amounts of starch allergen escape from paper car tons into milk sauerkraut and frozen foods Corn and corn syrup sensitivity also has been stressed by Randolph and others These al lergens find their way into many processed foods In regard to the incidence of corn sensitivity Loveless[37] reports clinical symptoms from ingested corn in 0 16 per cent of allergy patients as determined by a poll of allergists treating 15 000 patients in contrast to an inci dence of 16 to 30 per cent reported by Rinkel Randolph Rowe and Crandall

Food Adjuvants

Vegetable Gums The vegetable gums karaya tragacanth and acacia (gum arabic) are used in the food industry to add bulk thick ness and heaviness to foods which would otherwise require starch agar or other thickening agents such as flour These colloid sub stances are substituted because they are cheap and serve the purpose for which they are intended They are used in fillings of candies processed Cheddar cheese cream cheese whipped cream cake icing tooth pastes commercial potato salad mustard jello wheat cakes and so forth as shown in Table 8

Spices Condiments and Other Food Accessories

Spices and other food accessories although not generally reported as causes of allergic disturbances may nevertheless be potent factors in producing cutaneous gastrointestinal and other allergic reac tions The majority of these spices contain various chemicals as well as oils and may be primary irritants We may thus have as with the gums the twofold action irritative and allergic

Included among the spices are mustard pepper ginger cinna mon cloves nutmeg and thyme with mustard the outstanding of fender In addition to being used in foods mustard is employed as a counterirritant in the form of pastes and plasters which may

account for urticaria and asthma in some cases In foods such as mayonnaise salad dressings catsup and sausage even an infinitesimal amount of mustard may produce severe allergic reactions

Levy[38] reported an unusual instance of bronchial asthma in a boy nine years of age who was clinically sensitive to fennel and fennel seed

The importance of vanilla almond mint and peppermint as food accessories should not be minimized in allergic diagnosis

TABLE 8 FOOD SOURCES OF GUM ALLERGENS

Karaya gum	Gum arabic	Tragacanth
Commercially prepared potato salad	Cake icing mixtures	Commercially prepared salad dressing
Salad dressing	Soft fillings in candies	Gravies
Mustard	Certain brands of marsh mallows	White sauce
Whipped cream		Whipped cream
Ice cream		Processed Cheddar cheese
Charlotte russe		Certain brands of chewing gum
Griddle cakes		
Soft fillings in candies		
Cake icing mixtures		
Cheddar cheese		
Swiss cheese		
Packaged cream cheese		
Tooth paste		
Certain chewing gums		

Miscellaneous Foods

Coffee Lupton[39] described a case of cheilitis due to coffee It also caused epigastric and substernal discomfort and eructation

Alcohol and Alcoholic Beverages As a result of experimental studies Dees[40] concluded that allergic and histamine wheals are increased after ingestion of alcohol She believes that in so called alcohol sensitive persons the ingestion of alcohol brings a subclinical reaction to a clinical level Many of the reported reactions to specific alcohol beverages reviewed by Dees appear to be due either to extraneous substances present in the beverage or to substances from which the beverage was derived A patient sensitive to grape and grape products including wine was reported by Brown[41]

Gelatin Ratner and Crawford[4] basing their conclusions on experiments with anaphylaxis indicate that gelatin is nonanaphylactogenic In their opinion any allergy that might be attributed to

gelatin is due to contamination with blood elements of the species from which it is derived But this conclusion has been challenged by Mendez and Hughes[43] who showed that gelatin possesses anti genic properties of its own and reported a case of sensitivity to it

Buckwheat Clinical sensitivity to buckwheat has been re ported[44 45] Symptoms may be caused by either inhalation or inges tion Ordman[46] described three cases of sensitivity to inhalation of the flour *two of the patients being sensitive also to its ingestion*

Mushrooms A case of contact dermatitis due to mushrooms was reported by Hopkins[47] Skin and patch tests were positive

Beet and Beet Sugar Among 28 cases of anthocyaninuria 26 were found by Zindler and Colovos[48] to be related to beet allergen Five *of these patients were sensitive to beet sugar Randolph and Rol* lins[49] reported four cases of sensitivity to beet sugar in three of which there was also sensitivity to monosodium glutamate of beet origin The latter is a condiment derived from beet wheat corn or soy bean It is widely used as a flavoring agent in the preparation of many foods and can easily be overlooked

INFUSIONS

Kelvin and Schless[50] reported the death of a six day-old infant allergic to milk Death was attributed *to an intravenous infusion of* Amigen a derivative of casein They postulated that it could con tain proteoses of casein which may have caused the anaphylaxis Coppinger and Goldner[51] reported another fatality following the intravenous administration of Amigen

Dextran although not a food is a polysaccharide derived from sucrose through fermentation by the microorganism *Leuconostoc mesenteroides* Its use as a plasma expander in the treatment of shock has been advocated Reactions of an allergic nature some of which were alarming—severe urticaria dyspnea cough and shock—have followed its intravenous administration in man [53]

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H Beecher Chapin

PULMONARY FUNCTION TESTS IN THE PRACTICE OF ALLERGY

Pulmonary function tests which have had increasing use in the medical armamentarium can provide helpful information to the allergist in the management of certain allergic diseases It is the purpose of this chapter to discuss the tests available and to present the rationale for the use of those particular tests which may best be utilized by the practitioner

In the practice of allergy the clinician is confronted by those allergic diseases or diseases possibly related to allergy that require testing of the efficiency of respiration because they impair the respiratory apparatus Asthma is of course the primary disease with which the allergist is concerned Other diseases in allergy involving impairment of respiration may include periarteritis nodosa eosinophilic infiltration of the lungs such as Loffler s syndrome eosinophilic granuloma in the region of the thorax scleroderma disseminated lupus erythematosus and the pneumonitis of rheumatic fever

Pulmonary function tests are important in these diseases primarily because they indicate the degree of respiratory impairment and only secondarily because of their diagnostic value The practitioner may also employ them to discover early pulmonary dysfunction in patients with known allergic disease In addition the tests may prove a useful guide in establishing the severity of pulmonary involvement as a disease runs its course or in evaluating the usefulness of therapeutic measures designed to alter the course of the primary disease

process The tests may also prove the usefulness of such therapy in establishing efficient pulmonary respiration

The following tests done by a pulmonary function laboratory are designed to determine specific physical or chemical data

Circulation time
Treadmill exercise test
Chest measurements
Venous pressure
Determinations of lung volumes and capacities
Dimensions of the heart
Respiratory rate
Respiratory depth
Intracardiac pressures
Respiratory minute volume
Maximum voluntary ventilation
Expiratory and inspiratory velocities
Velocities of portions of forced maximal expiration

Compliance
Mechanical resistance
Alveolar gas uniformity
Helium distribution
Hemoglobin and hematocrit
Arterial oxygen content
Arterial oxygen capacity
Arterial oxygen saturation
Arterial carbon dioxide content
Arterial carbon dioxide tension
Arterial pH
Oximeter rise and rate
Oxygen consumption
Carbon dioxide elimination
Alveolar oxygen tension
Arterial oxygen tension

In addition the relationships between some of the various determinations listed serve as special indicators of pulmonary function Occasionally observations of the movements of the diaphragm observed at fluoroscopy may be useful as are roentgenologic studies of the lungs

To say that this multiplicity of riches available to the investigator of pulmonary physiology may prove unwieldly to the practitioner in his management of a particular case is not to cavil but merely to emphasize that there must be an understanding of the situations in which their use is of relevance and of the limitations of usefulness of all pulmonary function tests It is clearly apparent that no single test mentioned above can give a diagnosis of a disease entity [1] The tests when their results are abnormal merely indicate an alteration of function *The sum of these tests somewhat imperfectly describes* what pulmonary ventilation is That this sum is not the entire story is suggested by the necessity for the arbitrary division of the phases of respiration Thus it has become the custom to divide the pulmonary respiration process into roughly two phases The first of these phases is the mechanical (ventilatory) phase a defect in the function of which causes the symptom of dyspnea The second phase is the chemical physiologic and includes the diffusion of gases across the alveolar-capillary membranes and also the flow of pulmonary

capillary blood A defect in this phase is demonstrated mainly by the symptom of cyanosis [2]

The practitioner in his office is concerned mainly with tests involving the mechanical ventilatory phase not only because of their comparative ease of performance with simple equipment, but also because usually it is the ventilatory phase which is the first to become measurably altered in the pulmonary disease states with which the allergist is likely to be confronted It has been said that if the ventilatory phase alone is studied over 90 per cent of patients with pulmonary disease can be evaluated adequately This is because a relatively smaller defect of ventilation than of the chemical physiologic phase of respiration produces symptoms By the time a

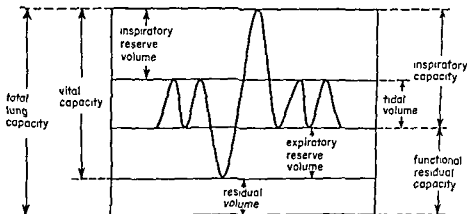


Fig 14 1 Divisions of lung volumes and capacities as related to normal respiration and to maximal inspiration and expiration

significant alteration of alveolar capillary function occurs ventilation is severely impaired [3] To put it another way cases of almost pure ventilatory phase insufficiency are not uncommon but cases of almost pure chemical physiologic respiratory phase insufficiency are rare There are of course cases in which insufficiency of both phases may be present in varying proportion In the diseases with which the allergist usually is concerned however it is ventilatory insufficiency that is dominant and *the ventilatory function tests are the first to show abnormality*

It is worthwhile to give a brief description of the ventilatory phase of respiration and the familiar descriptive diagram shown in Fig 14 1 is helpful in understanding this function

With this pictorial description of ventilation in mind a consideration of those types of defects which cause a change in the function

of ventilation is in order A knowledge of these defects and their causes as determined by anatomic and pathologic studies is necessary for the understanding of the rationale of the tests which have been devised to record the altered function occurring when a disease state such as asthma is present It has become the custom to describe these defects as restrictive and obstructive in type

Restrictive defect is secondary to destruction of or enchroachment on alveoli as by lung tumor pleural effusion surgical removal of lung or thoracoplasty

Obstructive defect is secondary to an obstruction to air flow in the air passages as in asthma emphysema polyp of a bronchus or drowning

This description of ventilatory function defects is a simplification but it is useful for the sake of clarity To obtain a more complete picture of the subject the problems of uneven alveolar ventilation the elastic properties of the lung and the thorax and mechanical resistance must be considered It is now possible to measure directly the specific resistance to breathing and these measurements may be obtained in the well equipped pulmonary function laboratory In general it may be said that the forces involved in ventilation depend on volume change and on the velocity of the gases moved The relationship of these factors to the tests to be described will be shown subsequently

To summarize it is with those diseases in which there is mainly ventilatory insufficiency that the allergist is usually concerned and the defect present in those diseases usually is obstructive in type

TESTS OF VENTILATORY FUNCTION

When a patient complains of dyspnea it is often necessary to attempt to determine whether there is a true mechanical interruption to air flow through the respiratory passages underlying the symptom or whether the cause of the symptom lies elsewhere The answer by the patient to the routine question of the medical student How many flights of stairs can you climb? illustrates the difficulty in evaluation of causation The patient s answer may be sometimes informative but if extreme impairment of pulmonary function is present in the large majority of cases the answer is uninformative or equivocal Since the symptom of dyspnea is a subjective complaint and there is no known absolute way of determining the threshold level of the dyspnea sensation on consciousness in differing individuals the difficulty inherent in the problem is obvious

Respiratory Rate The most widely used observation on the pul

monary apparatus is the frequency of respirations There is no doubt that if a patient complains of shortness of breath and the examining physician observes an increase in the patient s respiratory rate the physician will consider this fact of significance in correlating the subjective complaint with the observed finding but an increase in respiratory rate is caused by too many other factors such as fever or hysteria to make it of use in the search for a true ventilatory function defect

Capacity and Air Velocity Tests While there may be a normal vital capacity in the case of ventilatory insufficiency involving an obstructive defect as in asthma or emphysema the velocity of gases moved during the inspiratory and expiratory efforts of respiration may be slowed Thus the results of the tests measuring velocity such as the maximum voluntary ventilation (maximum breathing capacity) and the timed vital capacity (one second and three second vital capacity) may be lowered abnormally when a normal vital capacity is present Conversely in the case where there is a restrictive defect *such as lung tumor the results of the air velocity tests may be normal* when the vital capacity is lowered abnormally[1] Here again is seen the interaction of volume and velocity as concerned with the ventilatory type of defect in respiration

Vital Capacity If no other test of pulmonary function is performed by the allergist the vital capacity of patients with known or suspected pulmonary disease should be measured As stated above *however the test is of value mainly in revealing the presence of the* restrictive type of defect as in the destruction of alveolar tissue by tumor or by the processes causing emphysema The vital capacity may be decreased abnormally as well in other conditions such as paralysis of the diaphragm or kyphoscoliosis or where there is nerve pain The impairment of the vital capacity measurements by so many differing types of disease states limits its usefulness No allergist however who has done serial determinations of vital capacity over a period of months or years on an individual patient would discount the value of this test as a practical aid in following the course of disease

The test consists of having the patient expire slowly and completely into a spirometer after he has inspired to the limit of his capacity It is important that the vital capacity test be determined with a correctly calibrated instrument whether it is of the bellows or spirometer type The results obtained are of value when used in conjunction with the calculated normal vital capacity of the patient which is readily obtained from tables of normal values in standard textbooks or from tables furnished with the instrument It should

be remembered that normal vital capacity findings vary as much as 20 per cent from the average normal figures given in such tables A single determination cannot be considered abnormal unless it is 20 per cent below the calculated normal for the individual patient This fact makes it important that serial determinations be made since the *change* in the measurements is of more significance than the results of a single determination The calibration of the instrument whether bellows or spirometer should be checked from time to time to guard against error resulting from the usual wear and tear of general office use

It should be emphasized that the vital capacity test is most valuable when performed on the same patient repeatedly at appropriate intervals of a week or month in following the case of asthma or asthma with emphysema The value of the test is increased if a standard dose of a bronchodilator drug such as epinephrine is given by injection and the vital capacity determination repeated ten or twenty minutes after the injection so that the element of bronchospasm in the disease is ascertained Serial determinations of the vital capacity in chronic asthma both before and after the use of a bronchodilator drug undoubtedly are of value in following the course of the disease and in determining the efficacy of the therapeutic measures used

Tests of Air Velocity in Respiration It was the limitations of the vital capacity test that aroused interest in the development of a more informative and yet simple test of pulmonary ventilatory function Mainly because the vital capacity test is the measurement of a static volume it was postulated that a test capable of measuring the subject's maximum ventilating powers would be more informative Tests of the velocity of air moved in respiration when the subject is making maximum effort to ventilate were devised and these tests are an indication of the maximum amount of work or force that can be commanded by a subject for maintaining maximum ventilation[4] The standard test of this nature has been the maximum voluntary ventilation capacity test (maximum breathing capacity) which may be readily performed by means of a Collins vitalometer This test widely used in pulmonary function laboratories and of proved value as giving a good estimate of ventilatory reserve is considered unsuitable in allergy practice because it is felt that the method of performance tends to increase bronchospasm in the asthmatic patient and even to precipitate attacks of wheezing

Timed Vital Capacity Tests The so-called timed vital capacity test (the one second and three second vital capacity tests) has been found more useful for the allergist This test measures the velocity

of air during one forced maximal expiration of the subject during the stated time intervals and the results have been found to correlate well with the results of the voluntary ventilation capacity test Since the time of effort of the patient s ventilating during the test is short compared with that required in the voluntary ventilation capacity test there is less opportunity for increasing bronchospasm in the asthmatic patient The patient is instructed after a maximum inspiration to expire as rapidly and forcefully as possible into a spirometer to which has been attached a timing device (described by Gaensler[5]) which records the volume of air expired at the end of one second and three seconds In normal subjects approximately 83 per cent of the total vital capacity is expired at the end of one second and 97 per cent at the end of three seconds Similar measurements that are graphic may be obtained with a Gorrell spirometer by means of which the tracing of a forced respiration on a rapidly moving paper records the information This apparatus has the advantage of recording in a simple manner the entire inspiratory and expiratory phases on a sheet of paper which may be inserted in the patient s office chart and the required measurements of air velocity are determined easily from this tracing More expensive devices such as the pneumotachograph or electrical flowmeter are available and recently a device has been described utilizing the venturi tube principle

These tests are essentially measurements of velocity and it should be noted that the measurements are useful mainly from the standpoint of evaluation of pulmonary ventilatory insufficiency The findings should be considered in relation to the vital capacity as mentioned above and compared with the calculated or observed values for normal individuals of the same sex and age group as the patient under study Studies by the author and others[6] suggest that the mean velocity of air during forced maximal expiration of the entire expiratory phase is to be a more sensitive test than the timed vital capacity tests limited to one second or three second periods The mean velocity of air for the entire expiratory phase of course includes the vital capacity value as an integral part of the reading of the test

Whatever the device used to record velocity of air moved on one single maximum forced expiration after a maximum inspiration the results of this type of testing have been found useful in detecting pulmonary ventilatory insufficiency[1] It may be used not only in the quiescent periods of chronic asthma to measure pulmonary ventilatory insufficiency that may be present even though the patient does not complain of dyspnea but also during acute attacks of asthma

without fear of unduly increasing its severity Thus this test has particular merit in charting the improvement in the asthmatic patient when a specific therapeutic measure is under trial Cooperation of the patient is obtained readily when the simplicity of the method of

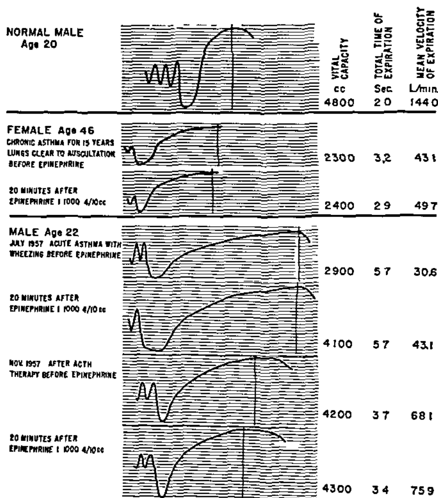


Fig 14 2 Tracings showing expiratory volume velocity rates of a normal patient and of patients with acute and chronic asthma

performing the test is explained to him The patient with severe psychoneurotic or psychotic tendencies whose test results would be suspect is easily identified by his manner of performing the test

For the performance of these timed capacity tests it is important

that a routine be established which is not varied from subject to subject The patient should be in the sitting position A nose clamp should be used to prevent escape of air through the nostrils when he expires into the apparatus He should not attempt the test until the method of performance is explained clearly to him Clothing should be loosened about the neck and artificial dentures removed from the mouth After a maximal inspiration the patient is instructed to expire as quickly forcefully and completely as possible into the mouthpiece It is customary to perform this procedure three times with a rest period of approximately five minutes between the tests the best result of the three tests being recorded The procedure is repeated after the injection of a bronchodilator drug to determine the amount of bronchospasm present Figure 14 2 illustrates tracings used to find mean velocities of air during forced maximal expiration as determined by means of the Gorrell spirometer on a normal subject and asthmatic patients It is to be noted in the male patient that although the vital capacity remained essentially unchanged as the patient s asthmatic condition improved under therapy the mean velocity of expiration showed a marked increase thus giving a better indication of the true condition of the patient

These tests of expiratory velocity are easy to perform and the equipment is suitable for office use It must be emphasized however that the person supervising the tests must be trained in their proper use just as a technician is trained for the proper performance of a basal metabolic rate test or a blood cell count which require practice and careful attention to detail for best results

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15

NEWER METHODS OF INVESTIGATION OF ALLERGIC STATES *

A question often asked the allergist is in essence By what mechanism do repeated injections of a pollen extract diminish clinical sensitivity? Or more succinctly stated How do allergy shots work? The several stock explanations some of which contradict one another are representative of the lack of basic knowledge in the whole field of allergy

This should not be too surprising when one considers that the concept of hypersensitivity became established only at the turn of the century and the first 25 years were devoted mainly to a rough clinical delineation of the phenomenon During that time comparatively few laboratory procedures were developed The anaphylactic reaction the Schultz Dale test and the precipitin test were used in animal work and for human beings the direct skin test and the passive transfer test became accepted procedures

During the past quarter century many new techniques of investigation have evolved which permit a more basic approach to the problems in this field Despite their laboratory nature these developments should be of interest to the practicing physician because directly or indirectly they will exert a marked influence on clinical medicine The following brief review is presented as a sampling of this work to illustrate the many new approaches that have become available It is not meant to be an exhaustive study and the exam

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ples and references chosen are simply those with which the writer is most familiar Details of the underlying principles can be found in such texts as Boyd s [1] and Kabat and Mayer s [2]

Ushering in the newer investigative era were three procedures which have provided data indispensable to much of the subsequent work All three have become well established They are (1) the ultracentrifuge of Svedberg and Pedersen [3] developed in the late 1930 s which made possible the precise determination of molecular weights of protein molecules (2) the quantitative precipitin test developed by Heidelberger and Kendall [4 5] which allowed calcula tion of the ratios in which antigen and antibody molecules combine and (3) the work of Landsteiner [6] and Pauling and associates [7 11] with hapten azoproteins which helped to clarify the nature of the chemical groups which confer antigenicity and enter into union with antibody

ELECTROPHORESIS

Electrophoresis another well established procedure has played a prominent part in serologic investigations since 1930 and several modifications of the original Tiselius method have made it adapt able to many purposes A supporting medium such as filter paper is now commonly used At the conclusion of the procedure the pro tein bands are made visible with a dye and the strip becomes a permanent record The paper may be oiled and scanned to produce the typical graph from which the relative amounts of each compo nent can be computed Small amounts of the various fractions can be recovered for other studies by eluting them from their respective positions on the strip Some technics employ more serum and sev eral layers of paper when this is desired Some workers [1 13] have used a large starch block as a supporting medium which allows several milliliters of serum to be subjected to electrophoresis after which the basic structure is cut into strips across the path of migra tion and the content of each is eluted The relatively new continu ous electrophoresis apparatus promises more help in making frac tions available in larger amounts [14] The material continuously drips onto a tab at the upper end of a sheet of buffer saturated filter paper with electrodes attached to each side As the material flows down ward the fractions migrate laterally to their respective positions and drip off the serrated lower edge of the sheet into test tubes

The various electrophoretic fractions have been widely studied for antibody activity The skin sensitizing antibody (reagin) from atopic persons has been reported in all globulin fractions although it is probably more prominent in beta globulin [13] Other human anti

bodies are principally gamma globulin. These include the blocking antibody induced by allergic desensitization, the antibody arising during horse serum sickness, the antibodies produced by immunization to disease and the isoagglutinins of the blood groups. The precipitating antibody produced in animals by sensitization is mainly in gamma globulin. However, in the sera of certain highly sensitized animals, after all precipitating activity has been removed, there remains a factor capable of sensitizing the human skin on passive transfer[15] and, like the human sensitizing antibody, this is found in all globulin fractions. Albumin has never been shown to have any antibody activity.

GEL DIFFUSION

The technic of gel diffusion has been used for only about 10 years, but its usefulness has made it widely favored. Whereas in the test tube precipitin reactions require optimal concentrations of antigen and antibody that are difficult to ascertain, when these substances diffuse toward each other in agar gel the diffusion automatically continues to the point of optimal concentration and the resulting complexes form an opaque line. Furthermore, each antigenic component in a mixture tends to diffuse at a different rate and to form a separate line. As Wodehouse[16] pointed out, this technic can reveal antigenic and antibody differences that were only simply foreshadowed by such other technics as chromatography and electrophoresis.

Oudin's earlier method[17] incorporated the antibody with agar in a test tube which then was covered with a solution of antigen, the components of which migrated into the agar. This method, with modifications, still has many applications.

A more popular variation devised by Ouchterlony[18] has been the use of a thin layer of agar on a glass slide or Petri dish. The substances to be diffused are put into depressions in the agar or into small cylinders set on the agar about 2 cm apart. Several combina*tions may be interdiffused, allowing a comparison in the behavior* of two or more antigen or antibody solutions on the same slide. Feinberg[19] and Ouchterlony[20] have recently presented excellent reviews of the practical details of this technic.

This method of study has been applied to pollen[1-3] and dust[4] extracts apropos of skin testing and desensitization. Although it had long been suspected that most grass pollens were similar, it remained for Wodehouse to sensitize rabbits to each of several grass pollens and then to set up various combinations for gel diffusion. When a rabbit's antiserum to the pollen of June grass was diffused simulta

neously with the pollens of June grass and orchard grass the patterns produced were almost identical This was also found true for timothy sweet vernal grass and red top but with Bermuda grass there was little overlapping This confirmed the clinical impression that desensitization to Bermuda grass must be handled separately from desentization to most other grasses The antigens of stinging insects have been similarly compared [5] and this test has been used extensively in the study of fractions of human serum in the normal and various disease states [6-9]

Germuth and associates [30] have performed diffusion studies ingeniously by substituting the cornea of the intact rabbit for the gel When they injected antigen and antibody into two different sites of the same cornea of normal rabbits they could demonstrate a line of precipitation between the sites When they injected antigen into the center of the cornea of a sensitized animal they obtained a line of precipitation concentric to the limbus Biopsy revealed an inflammatory reaction in the avascular connective tissue stroma at the line of precipitation

PASSIVE CUTANEOUS ANAPHYLAXIS

Passive cutaneous anaphylaxis (PCA) allows a semiquantitative study of the antigen antibody reaction in vivo The general principle has been utilized for several years but various refinements have been introduced and Ovary [31] has recently reviewed the present status of the technic Basically it consists of producing an antigen antibody reaction in the skin of an animal after passive sensitization This can be achieved variously by injecting both factors intradermally by injecting the antibody intravenously and then challenging with an intradermal injection of antigen or by injecting the antibody intradermally and challenging with intravenous antigen Ovary preferred the last method India ink or a similar dye injected intravenously with the antigen leaks out into the skin at the reaction site and the size and intensity of the stain signify the degree of the reaction The end point is taken as the least amount of reactant that will cause staining

Many of Ovary's studies utilized the combination of rabbit anti hen egg albumin versus crystalline hen egg albumin injected into guinea pigs but several other systems worked equally well not only in the guinea pig but also in the rat mouse and hamster This technic has allowed many observations in regard to the localized antigen antibody reaction such as the effect of antihistamines cortisone and denervation on the reactions and histologic study of the

reaction site Various fractions of antigen and antibody material can be compared Human antibody as well as that of animal origin may be used However even though some nonprecipitating antibody from human beings may give a positive result on the PCA test others may not regardless of the Prausnitz Kustner response Interestingly goat and horse antibody will not produce a PCA reaction in guinea pigs

Ovary has concluded that the passive cutaneous anaphylaxis reaction is due to cell fixed antibody in the skin and that histamine is the mediating agent

HEMAGGLUTINATION TESTS

The groundwork for in vitro detection of the nonprecipitating skin sensitizing antibodies (reagin) of human allergy was laid by Coombs[3] in 1945 when he devised the test for the blocking type of Rh antibody This factor did not cause agglutination but apparently saturated the combining sites on the red cells thereby preventing agglutination when the usual saline agglutinins were added For this reason it was called *nonagglutinating* or *blocking anti Rh antibody*

Coombs reasoned that these antibodies must be globulin molecules each of which was attached at some point to a red cell but was too weak or incomplete to bind a second red cell thus isolated complexes result He was able to bind these isolated units together to produce agglutination by the addition of rabbit antihuman globulin This became known as the Coombs test and several variations were subsequently devised

In 1953 Coombs and associates[33] demonstrated the presence of reagin in vitro Attaching egg albumin to red cells through a rather complex linkage they produced specific agglutination by next adding serum from persons sensitive to eggs and then adding a complex containing rabbit antihuman gamma globulin

Sehon Gordon and Rose[34] in 1957 simplified this test by attaching ragweed antigen to the red cells by way of bis diazotized benzidine solution and caused agglutination simply by addition of sera from patients who were sensitive to ragweed The test gave positive results with dilutions of serum as high as 1 1024 Thirty specimens of normal human serum gave negative results Sehon and coworkers noted the high degree of sensitivity of this test and concluded that the previous inability to detect these antibodies by in vitro tests was due to low concentration rather than to a hypothetical univalence

Witebsky and coworkers[35] utilized this principle in an investiga

tion of chronic thyroiditis and demonstrated the presence of circulating antibodies specifically directed against extracts of thyroid glands in 12 of 18 cases studied Instead of bis diazotized benzidine they treated the red cells with dilute tannic acid to cause the thyroid substance to adhere to them This technique had been worked out by Boyden [36]

The hemagglutination test has opened a wide field for the study of human antibodies which previously could be demonstrated only by the passive transfer test It may disclose the presence of antibody in many conditions in which an immune mechanism has been suspected such as postinfectious or postvaccinal encephalitis blood dyscrasia uveitis Guillain Barré syndrome glomerulonephritis and various collagen diseases It also may be found that certain cases of pancreatitis bilateral renal cortical necrosis and other diseases of idiopathic etiology are similarly connected

Essentially the same principle is involved in several tests devised to demonstrate a specific serum factor in cases of active rheumatoid arthritis [37] Compared with the above system the rheumatoid factor to be detected would correspond to the circulating antibody while the substance attached to the red cell acting as antigen is probably gamma globulin or a closely allied fraction This complex may be prepared in a number of ways If rabbit anti sheep erythrocyte serum is used it will unite directly acting as antibody toward the sheep cell but acting as antigen toward the rheumatoid factor Likewise a complex of human erythrocytes and gamma globulin may be obtained using Rh positive erythrocytes and blocking Rh antibody A third method consists of exposing tanned sheep cells to pooled human serum fraction II (of Cohn) which is mainly gamma globulin Interesting variations provide certain advantages by substituting other substances for the erythrocytes Thus Bozicevich and associates [38] used bentonite as the particulate matter while Singer and associates [39] achieved similar results with polystyrene latex particles

There are many variables which must be carefully controlled in each system but properly performed the tests are positive in 75 per cent or more of known rheumatoid cases while reacting with less than 5 per cent of nonrheumatoid sera Svartz and Schlossman [40] felt that they made the test more specific by using only the cold precipitable portion of the serum They and their coworkers [41] found that the main agglutinating activity was in a fraction which migrated to the fast gamma region of the electrophoretic curve and sedimented to 18 7 S in the ultra centrifuge The latter suggests a molecular weight of nearly 1 000 000 in contrast to 165 000 for most gamma globulins including the usual antibodies

TAGGING OF ANTIGEN OR ANTIBODY

Another line of investigation the tagging of antigen or antibody to follow its behavior in vivo has in the past met with varied success depending on how much the tracer substance altered the native material and how easily it could be detected and measured Various dyes and foreign chemical atoms such as arsenic have been used During the past decade this type of work has been expedited by use of radioactive isotopes since small amounts can tag a substance sufficiently for detection and measurement by the beta or gamma emissions without significantly altering its immunologic properties[4]

Utilizing this technic Dixon and coworkers[43] determined the half life periods of I^{131} labeled homologous gamma globulin for various species and found that they correspond closely with values obtained by other means Heterologous globulin was metabolized at the same rate as the host s own for several days then rapidly disappeared as antibody to it became detectable[44] If the antibody forming capacity of the animal had been destroyed by roentgen radiation the degradation of heterologous globulin continued at the same rate as that of homologous globulin On the other hand prior sensitization to the foreign globulin caused the challenging dose to disappear rapidly from the time of injection Dixon[45] also used isotope labeled antigen and demonstrated by autoradiography its localization in fatal anaphylaxis He challenged sensitized animals with a dose of labeled antigen and found large amounts of radioactivity in the bronchial walls of guinea pigs and in the pulmonary capillaries of rabbits

Another method of tagging which has recently come into wide spread use employs a fluorescent substance to demonstrate localization of antigen and antibody material in tissue sections Rabbit antiserum to a certain antigen is labeled with fluorescein 4 isocyanate this produces a green fluorescence when viewed under ultraviolet light[46] When tissue sections from animals that have been given the homologous antigen by injection are bathed with this fluorescent solution the antibody molecules become specifically attached to any of the antigen in the tissue thereby disclosing its presence Antibody in tissue sections can likewise be demonstrated by first washing the section with homologous antigen then with tagged antibody The antigen molecules cling to the antibody present in the tissues then in turn unite with the fluorescent antibody as it bathes the area

Using this technic Kaplan Coons and Deane[47] found that some antigens persisted in macrophages as long as 6 months while others disappeared within a few days Antigen was observed in the nucle

of certain cells[48] and they suggested that this nuclear invasion might cause an antibody producing cell to pass along some specific determinant factor to subsequent generations of cells thus accounting for prolonged immunity even in the absence of further antigenic stimulation

Coons and associates observed in the lymph nodes and the spleen the differentiation of a certain type of cell which gradually assumed the structure of a plasma cell[49] Only a few of these appeared after a primary injection but a secondary or anamnestic response was accompanied by large colonies of these cells packed with antibody as demonstrated by the fluorescence technic[50] He concluded that the plasma cell is the source of antibody and that whenever it is seen it is actively synthesizing antibody

CELL TRANSFER

Various technics for cell transfer have been devised in an effort to demonstrate which cells are involved in the production of antibody The principle is to isolate cells which have been exposed to antigen inject them into another animal of the same species and demonstrate a rise in antibody titer Certain control criteria must be met[51] Since some antigen is usually transferred with the cells the increase in antibody must occur sooner than would be expected for active immunization or the recipient should be irradiated sufficiently to prevent an active response to antigen The increase in antibody must be well out of the range of that which could occur from simple leaching out of antibody present in the cells at the time of transfer Transferred cells killed by freezing and thawing should elicit no response

Topley[5] demonstrated this phenomenon in 1930 with a saline emulsion of spleen from a rabbit previously given paratyphoid bacilli

In 1942 Landsteiner and Chase[53] accomplished it with peritoneal exudate cells from a guinea pig sensitized to picryl chloride Cells from the buffy coat of peripheral blood or from the spleen and lymph nodes gave similar results They noted that the effectiveness paralleled the lymphocyte content

The Harrises[54] obtained a marked rise in antibody titer by transferring cells predominantly lymphocytes teased from regional lymph nodes of rabbits given Shigella antigen by injection After producing a response with cells removed from a node within 10 minutes after antigen injection they obtained cells from unimmunized animals exposed them to the antigen in vitro and on injec

tion produced a significant antibody titer in recipients treated by roentgen rays The same workers [5] induced peritoneal exudates with mineral oil and exposed the cellular content to antigen in vitro On subsequent injection into other animals of the same species the increase in antibody was in proportion to the lymphocyte content of the exudate

On the other hand Fagraeus [56] found a significant rise of agglutination titer in tissue cultures of splenic red pulp from rabbits sensitized to Salmonella typhi This increase in titer correlated closely with the development of immature plasma cells No such rise occurred in cultures of lymphocytic tissue

The controversy as to whether lymphocytes or plasma cells are the site of antibody formation may be resolved as more is learned about the genealogy of the cells involved In an excellent review of the subject the Harrises [57] suggest that the two cells may be related either through a common precursor or by interconversion and indeed Dixon and Weigle [58] who injected sensitized lymphocytes into rabbits demonstrated that the rise in antibody titer correlated closely with the degree of replacement of the lymphocytes by plasma cells at the site of injection

CERTAIN OTHER APPROACHES

Numerous other approaches to the study of allergy should be mentioned although they embrace areas of investigation rather than illustrate any single method or technic For example since 1910 histamine has been known to play a part in many allergic reactions but only in the last 20 years have there been satisfactory methods for extraction and assay [59] so that reactions involving release of histamine can be compared satisfactorily and the role of that substance more accurately delineated

Schayer s extensive work [60, 61] with C^{14} labeled histidine is of particular interest Utilizing this tag which he devised he has observed the decarboxylation of histidine to histamine in various tissues and has identified and measured the excretory products of histamine in animals and man Other studies are unraveling the complexity of enzymes that metabolize histamine and their inhibitors and the role of the histamine rich mast cell is being avidly explored

More recently serotonin has captured the allergists attention because of the wheezing seen during acute attacks of the carcinoid syndrome [6] Interest was heightened when a marked increase of this substance was found in association with the reactions of hypersensitivity in certain animals [63] Reflecting the efficiency of newer labora

tory methods the metabolism of serotonin including its precursors and excretory products has been delineated within 10 years of its first identification[64] Small amounts are found in normal individuals and an intense study is being made of its variation in allergic and other disease states aside from the carcinoid syndrome[65]

The manipulation of adrenal cortical steroids comprises another large area of study In general these substances exert a protective effect against allergic reactivity whereas diminished adrenal cortical function enhances the allergic state[66] There are many discrepancies however and much remains to be learned about these mechanisms

Finally any well grounded consideration of antibody formation immediately plunges one into the whole field of protein synthesis with its myriad ramifications including nucleic acid activity protein structure adaptive enzymes virology and genetics

In this regard patients with agammaglobulinemia present a unique opportunity for investigation Good and his associates[67] have demonstrated the utilization of this naturally occurring phenomenon for many immunologic studies such as skin grafting immunization and resistance to disease and plasma cell activity Gale s observation[68] of protein formation by ultrasonically fractured cells depleted of their nucleic acid suggests another interesting approach particularly since the latter figures prominently in theories of antibody synthesis

Literally scores of other procedures are applicable to the study of hypersensitivity and it can be anticipated that in the next 25 years these methods will answer several of our current questions and probably raise many more The clinician will seldom be able to carry out any of these more intricate studies by himself but it is his responsibility to bridge the gap from the laboratory to the office Only by keeping himself well informed will he be able to cooperate profitably with the laboratory make clinical application of pertinent developments and in turn suggest further avenues of exploration

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PART THREE

MANIFESTATIONS AND FORMS OF ALLERGY



Murray M Albert | 16

HAY FEVER

Hay fever or more accurately *pollinosis* is an allergic disease characterized by the seasonal occurrence of attacks of excessive sneezing rhinorrhea nasal congestion itching and tearing of the eyes This symptom complex was first described in 1819 by John Bostock who called it summer catarrh In 1831 Elliotson first suggested that pollen was probably the etiologic agent In 1911 Noon demonstrated the practicality of the subcutaneous injection of pollen extract for the purpose of therapy by *desensitization*

ETIOLOGY

Hay fever may have its onset at any age from birth to seventy years However it most commonly begins between the first and third decades It occurs with equal frequency among males and females and it is generally estimated that there are between three and five million hay fever sufferers in the United States It is a malady which is confined almost exclusively to temperate climates

Two factors are essential for the development of hay fever The first is the inheritance of a capacity to become sensitized and the second is adequate exposure to the pollen to which the individual has become specifically sensitive In hay fever the capacity to become sensitized resides in the cells of the nasal mucosa which is called the *shock tissue* (see Chap 2) In asthma the shock tissue is the bronchial mucosa The age of onset of hay fever depends on the degree of inheritance The stronger the inheritance the earlier the onset of

symptoms There also seems to be a tendency to transmit the specific allergic manifestation Parents with hay fever are more likely to transmit hay fever to their offspring The degree of contact with pollen is often a factor in determining the time of onset of hay fever Undoubtedly exposure to abundant amounts of pollen such as occurs in the country will hasten it Not all types of pollen are capable of producing hay fever Certain characteristics as outlined by Thommen are essential

1 *The pollen must contain a specific excitant of hay fever* Pine pollen which like ragweed is abundant buoyant and wind borne does not produce hay fever since it lacks a specific excitant

2 *The pollen must be anemophilous or wind borne* Colorful plants such as goldenrod rose sunflower dandelion and daisy which are insect pollinated are of minor importance as causes of hay fever

3 *The pollen must be produced in sufficiently large quantities* Wind pollinated plants fulfill this criterion

4 *The pollen must be sufficiently buoyant to be carried considerable distances* The specific gravity and form of tree pollen grass pollen and weed pollen meet this requirement

5 *The plant producing the pollen must be widely and abundantly distributed* Although almost every important hay fever–producing species is found represented in the flora of New York State for instance only a few trees grasses and weeds are abundant enough to cause hay fever (see Appendix II)

There are several additional factors which determine the concentration of pollen in the air at any one time The amount of sunshine or rain the humidity the direction and velocity of wind and various atmospheric changes greatly influence the amount of pollen in the air Symptoms are aggravated when high winds expel more pollen into the air They are diminished when excessive humidity or rain lower the pollen content of the air Sunshine stimulates the anthers to open and discharge pollen into the air this usually occurs between 4 and 8 A M which explains the fact that most hay fever patients experience their worst symptoms in the early hours of the morning

There are three well defined hay fever seasons on the eastern seaboard

1 *Spring hay fever* which is caused by *tree pollen* and runs from the latter part of March until early June

2 *Summer hay fever* which is caused by *grass pollen* and lasts from the latter part of May to the latter part of July

3 *Autumnal hay fever* which is caused by *ragweed pollen* and lasts from the middle of August to the end of September

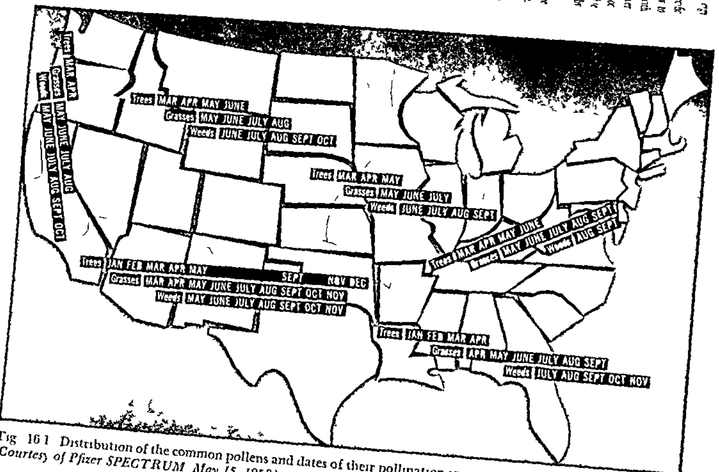


Fig 16 1 Distribution of the common pollens and dates of their pollination in various sections of the United States (*Courtesy of Pfizer SPECTRUM May 15, 1958*)

Figure 16 1 shows the distribution and dates of pollination of the common pollens encountered in the United States

PATHOLOGY AND SYMPTOMS

The histopathologic changes observed in nasal tissues of patients suffering from hay fever are characteristic of the allergic reaction and consist chiefly of pronounced edema and eosinophilic infiltration of the mucous membranes

The commonest symptoms of hay fever are paroxysmal sneezing nasal congestion rhinorrhea lacrimation and itching of the eyes The onset may be gradual or quite sudden depending on the degree of exposure to pollen When the onset is gradual the attack is usually preceded by a mild sensation of itching and burning of the eyes or mild irritation of the nose or itching of the palate Hay fever attacks frequently are of sudden onset ushered in by a violent exhausting paroxysm of sneezing especially in the early morning hours when there is a sudden increase in the concentration of pollen Marked nasal congestion and profuse rhinorrhea usually follow the sneezing paroxysms There is a sense of fullness in the ears Itching of the eyes marked congestion of the conjunctive profuse lacrimation and photophobia may or may not accompany the nasal symptoms Itching of the palate and the inner ear is a most annoying symptom As the attack progresses the nasal mucosa becomes highly sensitive and responds with sneezing to stimuli which were previously innocuous such as the slightest draft strong odors or minute amounts of dust

Many patients suffering from hay fever also complain of various constitutional symptoms such as lassitude loss of weight loss of appetite drowsiness constipation insomnia etc These symptoms are quite often due to the self administration of antihistaminic drugs

In some patients the ingestion of certain foods during the hay fever season produces an aggravation of the nasal symptoms This is particularly true of the pitted summer fruits shellfish corn etc In most cases these foods are well tolerated at other times of the year or cause relatively mild discomfort

Hay asthma (asthma caused by pollen) is a distinct form of pollen sensitivity not accompanied by nasal or ocular symptoms It recurs seasonally like hay fever This type of asthma is not very common More commonly asthma occurs as an accompanying manifestation of hay fever or as a complication of hay fever The type of asthma which accompanies hay fever usually develops after several seasons of

nasal symptoms It may be preceded by an irritative cough and a sense of tightness of the chest It usually begins in the second or third week of the hay fever season is probably due to the action of inhaled pollen on the bronchial mucosa and subsides at the termination of the hay fever season In some asthmatic patients symptoms may continue beyond the pollen season and gradually become perennial in nature In these cases other factors than pollen such as molds infections or physical agents prolong the asthma

DIAGNOSIS

The clinical or symptomatic diagnosis of hay fever is easily made from the history alone The seasonal recurrence of sneezing nasal congestion rhinorrhea and itching of the eyes and the presence of a positive family history of allergy are conclusive evidence of the presence of hay fever

Further inquiry should be made as to the exact period when symptoms occur in order to determine which pollens are the likely offenders The patient should be further questioned to determine whether there are other allergic manifestations such as food sensitivity urticaria eczema nonseasonal rhinitis migraine coughing or wheezing The proper management of associated allergic manifestations frequently determines the success or failure of hay fever treatment

The specific diagnosis of hay fever is based on the skin test The skin *and mucous membranes of almost all individuals who suffer* from hay fever contain reaginic antibodies which react in the presence of the specific pollen antigen

There are two methods of skin testing the scratch method and the intracutaneous method as previously described in Chap 12 For the diagnosis of hay fever the scratch test is adequate It may be performed with either dry pollen or a concentrated liquid extract It does not require any specialized skill and is much the safer method for the general practitioner Should a large reaction result the material can be quickly wiped off the skin With the intracutaneous method a small quantity (0 01–2 ml) of sterile pollen extract is injected into the uppermost layer of skin producing a small wheal The reaction can be read within ten minutes The intracutaneous technic is preferred by most allergists since by this method using serial dilutions of pollen extracts it is possible to determine quantitatively the degree of skin sensitivity This affords some measure *of the patient s tolerance for pollen dosage*

Employing quantitative tests makes it possible to classify the ma

jority of hay fever cases according to the method of Cooke into four groups as described in Chap 56

In hay fever in contradistinction to other allergic diseases a positive skin test is almost conclusive evidence of clinical sensitivity However it must be remembered that a positive skin test may indicate present past or future sensitivity A positive skin test for hay fever is significant only when it can be correlated with a clinical history of hay fever symptoms during the pollination period of the specific pollen During the course of routine skin testing with pollens many patients will show positive reactions to ragweed grass plantain and trees yet their symptoms may be confined only to the period of ragweed pollination The positive reactions to the others indicate that in the future they may also develop true clinical sensitivity to these pollens Contrariwise there are other patients who although they have lost all clinical signs of hay fever retain their skin sensitivity to pollen

In the small percentage of cases in which skin tests with pollens yield negative results in the presence of a definite seasonal history or in which there are perennial symptoms without apparent seasonal aggravation ophthalmic and nasal tests with dry pollens or with pollen extracts may be employed for confirmation

In the differential diagnosis hay fever must be distinguished from the common cold vasomotor rhinitis perennial allergic rhinitis and vernal conjunctivitis (see Table 9)

TABLE 9 DIFFERENTIAL DIAGNOSIS OF HAY FEVER

Features	Hay fever	Perennial allergic rhinitis	Vasomotor rhinitis (non sensitive)	Infectious rhinitis
Nasal secretions	Watery profuse colorless	Watery profuse colorless	Watery scant	Progressively thickening yellow
History of allergy familial personal	Present	Present	Usually absent	Absent
Sneezing	Marked	Moderate	Slight	Slight
Nasal congestion	Mod to marked	Mod to marked	Marked	Marked
Eye symptoms	Present	Present	Absent	Absent
Onset	Rapid	Rapid	Rapid	Gradua
Duration	Weeks	Hours to a few days	Hours to days	3 to 10
Nasal eosinophilia	Present	Present	Absent	Neu c
Positive skin tests	Yes	Yes	None	Noi

COURSE AND TREATMENT

Once hay fever has occurred it will recur each year at the same season if there is exposure to the specific pollen There is no way of determining for how many years hay fever will last In a small number of cases spontaneous cures are observed after a few seasons Most cases last more than ten years although there is a tendency for the symptoms to abate in the later years In some instances there may be a free interval for a few years followed by recurrence of symptoms

The treatment of hay fever is both symptomatic and prophylactic Prophylactic treatment consists of the subcutaneous administration of progressively increasing doses of pollen extract in an effort to increase the patient s tolerance for the specific pollen to which he is sensitive

Having determined the specific pollen or pollens which are causing symptoms it is essential to use a potent stable extract for the treatment Where two different species of pollens are required for treatment as for example ragweed and grass it is best to employ two separate extracts rather than a mixture The dosage to be administered is entirely dependent on the tolerance of the patient (see Schedule of Doses in Chap 56)

A rough estimate of the patient s tolerance can be elicited by performing an intracutaneous test with the weakest concentration of extract contained in the commercial packages Thereafter three concentrations are employed in multiples of ten the strongest being 100 times the concentration of the weakest If standardized on the basis of total nitrogen these would be 0 001 mg N 0 01 mg N and 0 1 mg N As the initial dose 0 1 or 0 2 ml of the most dilute extract is injected and the subsequent doses are increased by 0 2 ml until 1 ml is reached Thereafter the second concentration is employed and the process is repeated When the third concentration is reached doses are increased in multiples of 0 1 ml and the patient is carefully observed for any untoward reaction Before the onset of the season the patient should receive the maximum amount of pollen extract that he can tolerate without developing a marked local or systemic reaction It should be emphasized however that clinical results from treatment are not dependent on the amount of pollen extract which has been administered Patients who can tolerate only small doses often obtain more satisfactory results than those who tolerate large doses This illustrates the necessity for individualization of dosage rather than adherence to any set dosage schedule

There are three methods of hyposensitization therapy preseasonal coseasonal and perennial

1 *Preseasonal therapy* is instituted three to four months prior to the onset of the season Injections are usually administered every four to seven days so that the optimum dose is reached before the pollinating season begins Between 15 and 20 doses are usually necessary Preseasonal therapy may be terminated at the onset of the pollen season or treatment may be continued coseasonally During the season dosage is sharply reduced since the patient is inhaling considerable amounts of pollen from the atmosphere and it is possible for the treatment to aggravate the symptoms rather than alleviate them The maximum dose tolerated should be reduced 30 to 50 per cent or more during the season or discontinued completely if there is suspicion that it is causing an exacerbation of symptoms

2 *Coseasonal therapy* alone is reserved for patients who present themselves just prior to or during the pollen season It is possible to afford these patients some relief by the daily administration of vary small doses of pollen extracts either subcutaneously or intracutaneously It is advisable to use very dilute pollen extracts and not to attempt to reach any sizable dose

3 *Perennial treatment* consists of continuing pollen therapy after the termination of the season When the maximum dose which had been reduced during the season is again attained after a series of weekly injections the time interval between injections is first increased to two weeks then to three weeks and finally to four weeks if the patient can tolerate this interval between injections This schedule is maintained all year round until the season when the dose is diminished The perennial method has the disadvantage that the incidence of constitutional reactions is greater However most allergists believe that chances of cure are much greater under perennial therapy

Constitutional reactions of the immediate or delayed types may follow pollen therapy The symptoms vary in severity and range from excessive sneezing and itching of the eyes nose and palms to generalized urticaria angioneurotic edema coughing wheezing and dyspnea Since most constitutional reactions occur shortly after an injection it is advisable for the patient to remain in the physician s office for a short while after each treatment The treatment of constitutional reactions is dealt with in Chaps 56 and 61

The efficacy of specific pollen hyposensitization therapy is very difficult to evaluate accurately because there are so many variable factors The lack of uniformity in the preparation of pollen extracts the variation in dosage schedules and the lack of a standard for estimating the degree of relief obtained render it impossible to arrive at accurate statistics The general impression of most specialists

in the field seems to be that about 90 per cent of the cases of early hay fever and about 80 per cent of the cases of late hay fever ob tained satisfactory results from specific therapy

The commonest causes of failure are the use of improper pollen extracts because of an incorrect clinical diagnosis the employment of stale deteriorated extracts which have not been under refrigeration overdosage or underdosage and the failure to recognize and con trol other nonpollen sensitivities which the patient may have In spite of the failures encountered with specific pollen therapy it is well to remember that over 30 per cent of the untreated hay fever patients subsequently develop asthma and pollen asthma is more preventable by specific therapy than hay fever

Palliative or symptomatic treatment in the form of nose drops antihistaminic drugs cortisone and ACTH is much more efficacious when used with specific treatment than when used alone The use of these drugs in allergic diseases is discussed in Chaps 57 and 58

The percentage of failures or poor results from specific therapy can undoubtedly be reduced to a minimum by a careful analysis of each case

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ALLERGIC RHINITIS AND NASAL POLYPS

One of the most distressing manifestations of allergy in the upper respiratory tract is the combination of symptoms known as allergic rhinitis The symptoms consist of paroxysmal sneezing nasal obstruction watery nasal discharge and itching When these occur during the hay fever season and are accompanied by positive skin reactions to pollens the condition is known as seasonal allergic rhinitis or hay fever When these symptoms occur throughout the year with no relation to the pollen seasons the condition is termed perennial allergic rhinitis

The present discussion excludes hay fever which is discussed in Chap 16 and is limited to perennial allergic rhinitis A more precise term would be *perennial atopic rhinitis* to indicate that it is included in that group of diseases which are subject to hereditary influence

DIAGNOSIS

As with all other allergic illnesses one of the most important diagnostic tools is a thorough and detailed history In almost all instances it will be found that there is a positive family history of allergy establishing the existence of atopy Very frequently there is an associated allergic illness such as asthma hay fever urticaria eczema or migraine Symptoms consist of paroxysmal attacks of sneezing accompanied by nasal obstruction and profuse watery nasal discharge They are more pronounced in the early morning hours and

toward evening On physical examination the nasal mucous membranes are pale boggy and bluish purple in color The turbinates are markedly engorged and together with the abundant mucoid secretion produce almost total nasal obstruction Quite often there are polypoid changes present and even complete formation of nasal polyps

The diagnosis is sometimes made more difficult by the existence of a superimposed infection or sinusitis For proper evaluation of these factors it is often necessary to repeat the examination on several occasions

DIFFERENTIAL DIAGNOSIS

In the presence of a rhinitis it is necessary to decide whether or not the condition is allergic The clinical history is often misleading and the physical appearance of the nose is not always diagnostic Very often certain conditions will result in a pale boggy wet nasal mucous membrane which simulates an allergic rhinitis yet no evidence of hypersensitivity can be found and an allergic investigation will be fruitless For example the excessive use of vasoconstrictor nose drops in a nonatopic individual will cause a similar picture In such a case the mere cessation of nasal medication is sufficient to cause the complete return to normal of the abused mucous membrane Certain endocrine dysfunctions such as hypothyroidism also will frequently result in a similar appearance of the nasal mucosa and an acute primary nasal or sinus infection in a nonatopic individual may result in a mucous membrane that will vary from intense red to the same pale boggy mucosa just described

In all these instances the proper study of the nasal secretions according to the technic described by Hansel[1] may be of great help in the diagnosis In our experience the nasal smear in an active allergic rhinitis tends to show a predominance of eosinophils In those conditions where atopy does not play a role the nasal smears are not likely to contain eosinophils A positive nasal smear denotes excitation of the nasal shock tissue in an atopic individual That excitation may be specific as in sensitivity to pollens foods and inhalants or nonspecific as in the atopic individual whose nose is irritated by perfumes chemical irritants physical factors or mechanical stimulation

The nasal smear if done repeatedly during the time the patient is under observation can be a reliable guide to the progress made in the management of a patient with allergic rhinitis When the patient is having active symptoms the nasal smear tends to be positive As the offending inhalant and food factors are eliminated the degree

of nasal eosinophilia may diminish and with the clearing of symptoms the smears may continue to be free of eosinophils With exposure to a specific food or inhalant the smear again becomes positive

TREATMENT

Treatment depends on the determination of the specific etiologic excitant The etiologic diagnosis must be made by means of history skin testing elimination diets and therapeutic or clinical trial The methods used and the interpretation of results are exactly the same as in other allergic illnesses

Wherever possible the offending allergens whether inhalants or foods should be eliminated or avoided If this is not possible or practical then methods of desensitization must be employed The technics are identical with those employed in asthma or other allergic conditions (see Chap 56)

Temporary symptomatic relief may be obtained with the use of oral ephedrine products or antihistamines Local medication particularly strong vasoconstrictors should be avoided because of the danger of nose-drop addiction and the development of rhinitis medicamentosa Chemical cauterization zinc ionization and other measures which destroy viable tissue are to be condemned Nasal surgery is rarely if ever indicated in allergic rhinitis Steroids when used judiciously can be of great help in obtaining quick relief of symptoms while the etiologic factors are being determined Local use of the steroids has not been too effective

NASAL POLYPS

Nasal polyps have for many years been considered to be the result of inflammation sinus suppuration or infection In 1933 Kern and Schenck[2] were the first to point out the importance of allergy in the etiology of nasal polyps Despite their findings nasal polyps continued to be treated by surgical methods without regard to the possible mechanisms of their formation In recent years it has become increasingly evident that there is a close relationship between allergy and nasal polyps It would be more correct to consider nasal polyps as a complication of allergic rhinitis

A study of over 400 patients with nasal polyps revealed the following findings

1 A majority of the patients with polyps had a positive family history of allergy

2 Approximately one third of the patients had atopic nasal symp-

toms alone (hay fever and allergic rhinitis) About one fifth had atopic pulmonary symptoms alone *i e* asthma About one half had coexisting nasal and pulmonary symptoms The fact that such an overwhelmingly large percentage of patients with nasal polyps had as primary diagnoses such classic clinical expressions of the atopic state as asthma hay fever or allergic rhinitis would *tend* to corroborate the findings of Kern and Schenck that mucous polyps are extremely common in allergic conditions of the respiratory tract

3 Eighty five per cent of all the patients with nasal polyps showed an excess of eosinophils in their nasal secretions

4 In a large number of cases histologic sections of surgically removed polyps and biopsy specimens of nasal polyps were examined There was a predominance of eosinophils in every case

5 Intracutaneous skin testing was done in all cases Significant positive skin reactions were obtained in 60 per cent of cases indicating that reagins are not a necessary prerequisite to the formation of polyps This is about the same percentage of positive skin tests as is normally found in atopic respiratory conditions

6 Frank infection of the nasal accessory sinuses was absent in three fourths of all cases This would suggest that polyps *can* develop in the absence of infection

7 A surprisingly large number of polyps were reversible It was found that in certain atopic patients who were normally free of polyps nasal polyps would appear only during the hay fever season and would disappear spontaneously after the symptoms of pollenosis had subsided

In another group of atopic patients in whom polyps were normally absent nasal polyps would appear concurrently with an upper respiratory infection and would disappear spontaneously when the infection had subsided

A group of patients in whom asthma was the primary complaint and who also had nasal polyps were treated with ACTH and cortisone There was in addition to alleviation of the asthma regression or total disappearance of the nasal polyps

In another group of patients with nasal polyps standard allergic management was employed including the removal of offending foods and inhalants There resulted a diminution in size or total disappearance of the nasal polyps

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THE COMMON COLD AND ALLERGIC RHINITIS

THE COMMON COLD

The term common cold is generally considered to be a catch all designation for a host of undifferentiated respiratory infections which show clinical similarity in some degree Collectively these so-called minor infections constitute a major public health problem In terms of absence from work or school and resultant lowered productivity their annual cost to the nation reaches several billion dollars [1] In addition they frequently precede and perhaps aggravate more serious illnesses such as sinusitis and pneumonia and a number of chronic disorders of the respiratory tract They are also hazardous and may lead to fatalities in debilitated patients as in cardiac or kidney failure

By means of tissue culture technics employed in the study of common respiratory diseases in the last few years rapid progress has been made in a field of research that has long been a wasteland for investigators Recent advances suggest that illnesses of the cold type are caused by a host of agents—viral bacterial allergic and other factors the least of which may be psychogenic in origin

The Institute of Allergy and Infectious Diseases of the National Institutes of Health in collaboration with several other research centers has made extensive and productive studies of a group of respiratory viruses called the *adenoviruses* These prevalent parasites in man cause catarrhal inflammation of the mucous membranes

of the respiratory and ocular systems accompanied by follicular enlargement of the submucous lymphoid tissues and regional lymph nodes At least 25 serologically distinct viruses of the adenovirus group have already been isolated[3] Adenovirus infections are widely prevalent in the general population and are easily transmitted from one person to another They cause a large variety of respiratory illnesses and the symptoms are virtually indistinguishable from those of a simple cold influenza or streptococcal sore throat[4] The 25 adenoviruses are immunologically distinct but otherwise closely related

An effective vaccine against Types 3 4 and 7 of the adenoviruses has been developed These adenoviruses have received widespread attention since they are highly prevalent in military recruits and it has been adequately demonstrated that the vaccine will prevent many of the acute respiratory illnesses which have become a serious military and civilian health problem Adenovirus Types 1 2 3 and 5 are more prevalent in infants and children A vaccine against these virus types may well prove useful in young children Work is now in progress to develop a prophylactic multistrain experimental vaccine against the entire group of adenoviruses and to determine the duration of protection in human beings At present there is no evidence whatever that any one of the currently used chemotherapeutic agents or antibiotics has any effect against the adenovirus infections

Recently two new distinct viruses hemadsorption viruses Types 1 and 2 which are unrelated to the group of adenoviruses were recovered from infants and children with acute febrile respiratory illness[6] by means of the hemadsorption technic in conjunction with monkey kidney tissue culture[7] Clinical studies have established the fact that the Type 2 hemadsorption virus can cause respiratory infection and illness in adults[8] The Type 2 virus used for the inoculum in adults was derived from an infant with acute laryngotracheobronchitis Hemadsorption viruses are probably responsible for a segment of the common respiratory illnesses

The adenoviruses however do not cause the nonfebrile running nose type of infection often called the common cold whose virus has not as yet been isolated nor are there as yet specific laboratory procedures to establish the diagnosis The assumption is that the infectious agent is a virus A successful host other than man and the chimpanzee has not been found[9] The only way in which it has been possible to infect human beings or chimpanzees has been by intranasal inoculations and the only site from which the virus has been secured from patients with colds has been the nasal mucosa It has

been impossible to transmit the induced colds from person to person even by the most intimate contact suggesting that artificially induced colds may differ from colds occurring naturally which seem to be infectious [10] The induced colds are somewhat milder than the natural colds The exciting agent of the common cold appears to be a virus about as small as the encephalitic viruses with a size of about 40 to 50 millimicrons about one half the diameter of the influenza virus

The virus of the common cold induces a very poor immune response and has no demonstrable antibody response There is some evidence in volunteers that the occurrence of an induced cold increases resistance to reinfection with the same inoculum for two weeks but not for three weeks In chimpanzees immunity to reinoculation often persists for as long as three months The incubation period in volunteers inoculated intranasally with bacteriologically sterile filtrates of nasal secretions obtained from patients with typical colds is from one to six days with an average of two to three days Experimental colds have been successfully induced in 55 per cent of the volunteers The virus inoculated intranasally can be recovered as long as twenty four hours before symptoms develop and may persist in the respiratory tract for as long as seven days from the onset of symptoms Occasionally it has been possible to recover a virus from normal persons without symptoms of the cold suggesting the possibility that there are normal carriers Most workers now consider it possible that there are a number of different strains of the virus and think it likely that they do not immunize against one another In addition recent studies with volunteers have convinced some workers that a large number of common colds are due not to viruses *but to other factors not the least of which are those of psychosomatic origin* [11]

The investigators are rightly not concerned with the cold virus alone but with the virus in relation to the body s defenses Chilling and drafts appear to have no effect on susceptibility Natural colds nearly always occur through contact with someone else who has a cold The people in the United States collectively have about 400 million colds a year Children have about twice as many colds in a year as adults and the mothers of school children have twice as many as the fathers The school age child therefore must be considered an important carrier [1]

The common cold is essentially *a self limited disease However* in contrast to an attack of measles or scarlet fever it does not induce an immunity which will prevent the individual from having a cold soon again About 23 per cent of the population have colds four or

more times a year 60 per cent have colds two or three times a year and 17 per cent once a year or not at all The symptoms usually begin with chilliness malaise irritability and loss of appetite without fever Soon there may follow rhinorrhea sneezing and nasal obstruction The nasal discharge is at first watery then it becomes more viscous and purulent With the nasal obstruction there may be headache loss of sense of taste and smell mouth breathing and secondary pharyngitis and laryngitis The symptoms may persist for two to more than fourteen days or the cold may abort after only one day The common cold is itself minor but bacterial invasions frequently follow the initial infection and it is these secondary invaders that induce disorders of serious consequences such as sinusitis otitis media mastoiditis and pneumonia These complications occur because infection of the mucous membrane by many viruses results in considerable alteration in normal function and may cause destruction of the lining cells and denudation of the membrane When this occurs the tissues normally resistant to invasion by bacteria present in the respiratory tract become less resistant and infection with bacteria ensues It is also possible that viruses activate latent infections Fortunately these secondary invaders can now be controlled by the sulfonamides and antibiotics These chemotherapeutic and antibiotic drugs have however no effect on the virus of the common cold Of the 60 viral diseases in man only 4—psittacosis lymphogranuloma venereum trachoma and inclusion conjunctivitis all caused by large viruses—are effectively treated with sulfonamides penicillin or the broad spectrum antibiotics

The management of the common cold is at present largely symptomatic Adequate rest temporary isolation to prevent the spread of the infection to others an analgesic light diet and increase in fluid intake are prescribed For nasal blockage a mild vasoconstrictor such as ½ per cent NeoSynephrine or 1 per cent ephedrine is helpful Nasal medications containing antihistamines antibiotics or corticosteroids may produce harmful effects and sensitizations They may also prolong and intensify a common cold The sulfonamides penicillin and other antibiotics are not only useless for a viral cold but may actually endanger health since many individuals are allergic to penicillin and other antibiotics and experience severe reactions following their use [13-16] There is also the possibility of developing bacterial resistance to these drugs Cold vaccines composed of bacterial organisms comprising the flora of the nose and throat are of no value as protection against the common cold and are of doubtful value against its complications Control of or protection

against the common cold by air disinfection with ultraviolet light or glycol vapor and dust suppression procedures have been employed without effect[17] Attempts at increasing the resistance of the host by the use of vitamins special diets tonsillectomy irradiation of lymphoid tissue of the pharynx convalescent serum and gamma globulin have been similarly disappointing[18] Irrational treatments with purgatives diuretics diaphoretics medicated gargles and sprays and many varieties of cold tablets are being exploited despite the fact that physicians generally agree that these drugs do little to shorten prevent or cure a common cold[19]

Price[20] has recently isolated a new virus JH from patients with illnesses resembling the common cold and has reported that a vaccine prepared with this virus prevented illness among the children injected in an institution during an outbreak of upper respiratory infections Sufficient data are not yet available to permit adequate evaluation of this report

ALLERGIC RHINITIS

About half the people who suffer from symptoms resembling the common cold have their symptoms because of allergy and to the untrained observer these symptoms are indistinguishable from the syndrome caused by the cold virus The condition is known as allergic coryza or allergic rhinitis It is a condition of altered reactivity occurring in response to a specific stimulus There is no comparable response in nonallergic individuals In allergic rhinitis the mucous membrane of the nose is the shock organ[1] (see Chap 17)

There are certain characteristics and procedures which help to distinguish allergic rhinitis from the common cold of viral origin In allergic rhinitis the symptoms have a tendency to continue indefinitely and to flare up on contact with the allergen whereas the viral infections are self limited In allergic rhinitis a nonviable factor is the responsible agent usually an air borne substance such as pollen dust molds animal danders and face powders Occasionally a food is incriminated more rarely a drug The greatest cause of allergic rhinitis during the warm weather is pollen which produces the seasonal type of allergic coryza commonly known as hay fever There are about eight million hay fever victims in the United States who have symptoms resembling the common cold as well as itching eyes nose and throat during the warm weather They are sensitive to the pollens of trees grasses and weeds The most important and disabling types of pollen are produced by the high and low varieties of ragweed and are present in the air in high concentration from

about the middle of August to the first frost (see Chap 17) Allergic rhinitis cannot be transmitted to another person or even to a member of the family except possibly by inheritance [3]

At times we can differentiate allergic rhinitis from the viral cold by the difference in appearance of the nasal membranes The nasal membrane of the patient with allergic rhinitis is pale boggy and edematous not inflamed and is covered with a thin aqueous discharge whereas the nasal membrane of the patient with a viral cold is inflamed reddened and often coated with a mucopurulent discharge Eosinophils in the nasal smears are suggestive of allergy particularly if abundant but they are sometimes present when bacteria or their products are responsible for bacterial sensitization

TABLE 10 DIFFERENTIAL DIAGNOSIS OF HAY FEVER AND THE COMMON COLD

Diagnostic feature	Hay fever	Common cold
Seasonal incidence	Present	Generally absent
Other allergy	Common	Absent or coincidental
Family history of allergy	Usual	Absent or coincidental
Inciting agent	*Pollen*	*Virus or bacteria*
Contagious	No	Yes
Fever	Absent	Occasional
Positive skin reactions	Almost always	Absent or coincidental
Itching of nose eyes or palate	Usual	Unusual
Severe sneezing spells	Common	Rarely marked
Sore throat	Rare	Common
Conjunctival congestion or edema	Common	Occasional
Nasal excoriation	Very rare	Usual
Pale edematous nasal mucosa	Usual	Absent
Nasal polyps	Occasional	Usually absent
Congestion of the pharynx and nasal mucosa	Rare	Usual
Cervical lymphadenopathy	Absent	Common
Type of nasal discharge	Serous	Seropurulent
Eosinophils in the nasal secretion	Frequent	Absent
Antihistamines	Helpful	No effect

SOURCE *Modified from table by Sheldon Lovell and Mathews*

The differentiation between allergic rhinitis and the common cold due to a virus is based on three diagnostic procedures the history skin testing and the trial and error method If there is a history of allergy in the family or other allergies in the same patient or if there is a history in the patient of previous attacks of coryza on contact

with a specific substance in certain environments or at certain seasons of the year an allergic condition is strongly suspected Allergy must be considered seriously whenever coryza is associated with itching of the nose eyes pharynx soft palate or ears The presence of allergic rhinitis can usually be confirmed by positive skin reactions on skin testing with extracts of the suspected offending substance which is usually air borne such as pollen dust or animal danders The final proof is shown by the trial and error method of reproducing the symptoms when the patient is symptom free and then comes in contact with the suspected cause The diagnostic features of hay fever the seasonal form of allergic rhinitis and of the common cold are quite distinctive (Table 10)

The treatment of allergic rhinitis whether seasonal or nonseasonal yields effective results when the specific causes of the condition have been determined Elimination or avoidance of the offending substances will often clear up the condition When it is impossible or impractical to avoid an offending substance such as dust pollen or molds a process of immunization with extracts of the specific inhalant allergens is instituted which has the effect of building up a tolerance to the substances thereby eliminating or reducing the severity of the symptoms [5] Proper allergic management not only affords effective relief from the symptoms but also lessons the possibility of developing serious complications such as bronchial asthma sinus disease nasal polyps and progressive deafness The antihistaminic drugs are valuable agents for temporary relief of mild symptoms in allergic rhinitis [6] They greatly reduce the edema of the nasal mucosa However they can in no way be considered as a substitute for allergic treatment [9]

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W C Spain*

EXTRINSIC FACTORS IN BRONCHIAL ASTHMA

The extrinsic factors which act as specific excitants of bronchial asthma comprise a large and varied group into which practically every known cause except infection is placed Although diverse in origin and in characteristics these factors largely protein in construction may be classed according to their manner of entry into the tissues of the body as substances inhaled with the inspired air ingested as food or drug injected as heterologous serums biologic products antibiotics or insect sting venoms or anointed as unguents or topically applied medicaments Heat cold and light may also act as extrinsic agents of a physical type (see Chap 44)

Among the primary extrinsic factors none is more important than the group that excites symptoms by inhalation Present in the atmosphere in minute particulate and buoyant forms these substances are inhaled enter the body tissues by penetrating the upper and lower respiratory membranes and cause almost immediate symptoms of allergic coryza cough and dyspnea

Many of these inhaled excitants notably the pollens of certain trees and plants have the outstanding characteristic of being seasonal in occurrence producing discomfort only during the warmer months of the year and leaving the patient quite free of asthma during the winter The pollens of the hardwood trees are remarkable in their

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Deceased

ability to cause allergic dyspnea in April May and June even in city dwellers who rarely venture into the country

The grass family has a huge number of members whose pollens have the capacity to produce asthma by inhalation In the North eastern states during the months of May June and July the air teems with these granules Outstanding are those produced by timothy blue grass orchard low spear velvet sweet vernal and rye which seem to possess a common denominator a family trait which permits any or all of this group to disturb the grass pollen-sensitive patient Aiding and abetting the grass pollens is the pollen of plantain a weed of English derivation which is important as a causative factor in about one third of the grass pollen-sensitive cases Rarely plantain may be the sole cause of pollen asthma The pollen of sorrel is a less common cause of asthma during the early summer season

Preeminent however as the most notorious cause in producing pollen asthma is the ragweed plant Its outstanding importance is recognized by botanist allergist public health official and weed control expert who have combined forces in an effort to lessen the threat offered by it The giant and dwarf varieties flourishing in the Northeast share equally in causing each August and September asthma of such intensity and duration as to damage the health of the patient permanently Occurring as it does at the threshold of fall and winter ragweed pollen by inflaming respiratory membranes and lowering resistance encourages the development of complicating infections in the paranasal sinuses and in the bronchi Such secondarily induced inflammatory reactions may prove to have more damaging effects on the patient s respiratory system than the ragweed pollen itself (Further details on pollen will be found in Chap 16 Hay Fever and in Appendix II Botany and Allergy)

While ragweed flourishes in bright sunlight in airy open spaces a lesser but still important cause of seasonal asthma is the spores of molds and fungi which grow best in dark damp warm air and are identified with mustiness Molds flourish in infinite variety with many species difficult to identify Hormodendron Penicillium Mucor Cladisporium and Alternaria are members of this group which produces asthma chiefly during the late summer occasionally non seasonally (see Chap 43 and Appendix II)

While the agents eliciting seasonal asthma are relatively limited in variety being largely confined to the pollens and molds the causes of nonseasonal asthma are many Any dry particulate matter of vegetable or animal origin so attenuated that it can be raised and carried by the atmosphere is a potential producer of asthma The

sources of such excitants are the cotton linen kapok silk and wool of clothing and home furnishings the down and feathers of cushions and bedding the danders and salivas of domestic animals such as the horse dog cat rabbit and goat and occasionally tobacco insecticides and ground orris root a constituent of inexpensive toilet powders These substances are the components of house dust the microscopic litter of our routine domestic living against which the vacuum cleaner was devised It is the ubiquitous house dust which is supreme as a cause of inhalant asthma Despite our ability to recognize most of its ingredients it remains one of the most mystifying and baffling of the extrinsic factors since it contains allergenic substances which have so far defied analysis and identification

Occasionally occupational varieties of asthma may develop from the inhalation of dusts from other sources usually foods such as cereals nuts coffee tea spices malt and hops Such asthma often proves implacable and stubborn to treatment forcing the victim to abandon his occupation for another Detailed discussion of occupational asthma receives special consideration in Chap 22

In the exquisitely sensitive food asthmatic the odor of fish egg nuts or certain fruits or vegetables such as orange banana celery and onion may cause instant severe dyspnea

Usually however foods act as allergens by ingestion Any edible substance may cause asthma but egg milk seafood chocolate and nuts are the most important not only because of their high incidence as excitants but also because of the severity of the symptoms which they produce Bronchial asthma due to a food allergy may occur at any age but it is chiefly a problem of the first two decades of life Food sensitivity tends to disappear in later life While a significant characteristic of asthma due to inhaled substances is the promptness with which symptoms appear on exposure to the allergen this feature is present only in about half of the food cases In the other half the reaction is delayed and twelve to forty hours may elapse between the ingestion of the food and the appearance of symptoms a situation which renders identification of the food factor difficult By cross questioning by skin testing of the patient and by trial diet methods the offender may be discovered Despite these procedures the results in such cases are often disappointing

An extrinsic factor of increasing importance is an ever widening heterogenous group of drugs and therapeutic agents which may cause symptoms when inhaled but more often when ingested injected or applied topically Many members of this group are nonproteins becoming allergenic through their ability to link with body pro

teins to become drug protein conjugates Included in this group are aspirin quinine the sulfonamides and mercury (see Chap 46)

Allergic hazards may be produced by biologic agents organ extracts vitamin preparations heterologous serums in the form of antitoxins and antibiotic preparations of fungous derivation especially penicillin The occasional case of asthma due to wasp or bee sting is an injectant type of sensitization (see Chaps 45 46 47)

Absorption of the food excitant through the intact unbroken skin may in rare but important instances lead to asthma Egg beef nuts seeds banana citrus fruits celery white potato and other fruits and vegetables especially in food handlers may excite asthmatic attacks by contact with the skin Other extrinsic factors such as animal saliva silk mustard flaxseed and essential oils such as bergamot delphinium and wintergreen may cause asthma by surface contact or topical application

While a single extrinsic excitant such as pollen dust or egg may be the most important cause of asthma it is rarely the only one There may be associated sensitizations to various animal danders dusts nuts seeds or other foods Such multiple sensitization renders more difficult the identification of the principal specific cause or causes Furthermore the pattern of allergic response to the excitant may not be only respiratory From the same cause there may be an associated coryza dermatitis urticaria angioedema or gastroenteritis conditions which usually indicate a severe and complex allergic problem

Not all the extrinsic factors capable of producing attacks of bronchial asthma are primary A multiplicity of secondary agents may arouse intensify and complicate an asthmatic condition which actually springs from very different often obscure causes Such secondary factors may at times become even more important than the primary eliciting agents and may prove more difficult to control because of difficulty of identification and removal Traffic fumes chemical odors emanations of dry cleaning fluids naphthalene flakes paradichlorbenzene preparations paints and lacquers and gases from leaky heating cooking and refrigerating equipment may prove to be important excitants both in the home and in the shop The tensions and pressures of everyday existence the stresses and strains of acute or chronic emotional experiences in both child and adult may be the obstacle to improvement no matter how successful the identification of the primary exciting factors or how intelligent their handling (see Chap 8)

Extremes of temperature are secondary extrinsic factors which may readily aggravate an asthmatic condition basically due to other

causes At times however such factors seem of primary importance being the sole cause of asthma These cases are difficult to evaluate and even more difficult to treat successfully (see Chap 44)

The problems of diagnosis and of treatment are extensively discussed in Chaps 23 and 26 but here it may be mentioned that the extrinsic factors of importance in causing bronchial asthma may often be readily identified by careful and comprehensive questioning of the patient regarding the features of his asthmatic seizures The seizures are usually paroxysmal influenced by factors characteristic of the season of the environment or of the diet The cause and effect relationship may frequently be established without benefit of skin test since practically all the attacks due to substances inhaled and half of those due to substances ingested occur promptly on exposure to the excitant

The problem of extrinsic asthma may frequently be solved without extensive treatment or immunization schedules The simplest and at the same time the most effective measure against extrinsic *asthma is the removal from the patient s environment of the identified* or suspected exciting cause The replacement of bedding and bedroom furnishings which are under suspicion the banishing of pets and domestic animals the removal from the diet of suspected foods or foods notorious as causes of extrinsic asthma may solve many cases without skin testing procedures

Education of the patient as to the importance and significance of his extrinsic factors is essential but may prove difficult especially where his preferences or his emotions become involved His immediate and remote forbears may have been canny enough to utilize the lofts of their houses as their own living quarters reserving the ground floors for the shelter of their domestic animals but the city apartment dweller without discrimination and despite advice may welcome to his bedroom even to his bed one or more not so-clean licking and scratching animals Or he may realize the disturbing effect of a food but persist in retaining it in his diet even to excess Without removal of all known active extrinsic factors from contact with the patient even the most ambitious treatment schedules may prove unsuccessful

The asthmatic whose symptoms are due to recognized extrinsic factors of recent appearance is in that fortunate reversible stage when his distress may be altogether removed No complicating respiratory pathologic conditions or concomitant infections check his recovery Specific immunizing therapy may be required but no large list of drugs is necessary Ephedrine epinephrine antihistamines aminophylline and codeine may complete the list of required medi

cations The symptomatic treatment of asthma to be subsequently discussed is simple and uncomplicated in such cases (Chap 26)

Among extrinsic factors or factors from extrasomatic sources important in the causation of asthma there should certainly be included bacterial agents Responsible for causing infective asthma these are just as much of extraneous origin as are all the causative factors just discussed The pedantic physician could insist therefore that since all factors including bacteria capable of eliciting asthma originate outside the body all factors are actually extrinsic and there is no such thing as an intrinsic factor capable of causing asthma It is convenient however to regard only the noninfective agents—inhalants foods and drugs—as the extrinsic factors causing asthma and to regard the infective agents as the intrinsic (Chap 20)

20

Horace S Baldwin

INFECTIOUS FACTORS IN ASTHMA

The manifestations of asthma may be initiated by a wide variety of stresses and stimuli[1] As a result the problem of therapy has often resolved itself into the determination and control of the sum total of stimuli combined with drugs for symptomatic relief In analyzing the individual case of asthma not only the factor of hypersensitivity to inhalants such as pollens molds animal emanations and house dust must be considered (Chap 19) but also the factors of infection psychosomatic processes (Chap 8) bodily fatigue and the whole variety of experiences that make for the stress phenomena emphasized by Selye

In the present discussion the infectious factors comprise the main interest But it should not be forgotten that the other individual causative factors including hypersensitivities psychosomatic processes and other constitutional tendencies must be taken into consideration when evaluating the whole picture

That bacterial products are capable of producing active sensitization is clear from the work of Krause[3] and Dienes[4, 5] in tuberculosis Cooke[6] has described the basis for the belief that in asthma allergy to bacteria may be important Much work on the subject of bacterial allergy needs to be done and it is conceivable that future investigation may provide effective means for better management along immunologic lines of asthma due to infection In this discussion however practical management of infectious factors based on clinical experience will be emphasized

In evaluating infectious factors present in the asthmatic the his

tory is important Asthma occurring predominantly in the winter is apt to be involved with infectious factors Association with fever the expectoration of purulent sputum and leukocytosis with or without x ray evidence of pulmonary consolidation indicates an important infectious element in asthma A history of purulent nasal discharge or postnasal drip is very suggestive of infection In children the association of asthma with fever enlarged cervical glands earaches and sore throat points to infection in adenoids and tonsils

The physical examination of the asthmatic patient should start with the nose Here the presence of nasal polyps or pus in the nasal passages usually indicates infection Adenoid tissue in children often blocking the pharynx and damming back purulent secretion is important Examination of the chest will not necessarily indicate infectious factors since asthmatic wheezes may be similar whether due to infection or hypersensitivity to inhalants but the purulent character of the sputum and the bacteriologic examination will often show the infectious source of the exudate Naturally chronic bronchiectasis although not common in asthmatics is a primary indication of chronic infection

X rays of the nasal sinuses and expert rhinologic examination should be routine in practically every asthmatic just as every asthmatic should have a battery of the most important skin tests Cloudy antrums should be irrigated to determine the presence of active infection The nasopharyngoscope should be used to determine the source of nasal pus The sphenoid sinuses often the cause of intractable cough and asthma should be irrigated if there is any question In children x ray evidence of large adenoids confirmed by special nose and throat examination plus the association of asthma with colds and fever constitutes strong presumptive evidence that infected adenoids play an important part in keeping the asthmatic state active

In managing infectious factors in asthma the antibiotics have an important place Their chief use is in diffuse bronchial and pulmonary infection When the steroid hormones or ACTH are given alertness to the presence of active pulmonary infection and the prompt use of antibiotics may be lifesaving [7] In general it is preferable to give antibiotics orally Occasionally one antibiotic will be found preferable to another by means of cultures and sensitivity reactions with the various antibiotics Rarely is the use of antibiotics by inhalation preferable to adequate oral administration Frequently such inhalational procedures do more harm than good by irritating the bronchial mucous membrane The use of solutions of antibiotics in irrigating the nose and in particular infected antrums

may be a useful procedure Where adenoids are acutely infected antibiotics may relieve the acute attack In most cases however the infection is relieved only temporarily and the acute infection repeats itself until the infected adenoids are removed But here again in many cases this is not the final answer since so many of these children throughout adolescence will have diffuse hyperplasia of the pharyngeal lymphoid tissue with secondary infection after the main body of adenoid tissue has been removed In these cases repeated use of antibiotics may be useful in keeping resultant infectious bronchitis under control

Nasal surgery has an important place in the management of infectious factors in the asthmatic In children infected adenoids and tonsils should be removed Where septal deviation favors the retention of infection in the sinuses adequate submucous resection should be performed Where antrums are infected repeated irrigations may clear up the infection When improvement does not result the cutting of a window or permanent opening into the antrum is rarely a rewarding procedure Here the infection still remains in the antral membranes The operation of choice is the Caldwell Luc with exenteration of the infected tissue (see Chap 27 and 54)

Nasal polyps and widespread hyperplasia of the nasal membranes throughout the sinuses present a difficult problem and one for which there is no unanimous answer among allergists who are so often confronted with it It would seem that the best course with nasal polyps is to clear up the infection first by local treatment suction the use of local antibiotics and irrigation of infected antrums and sphenoids Nasal polyps which obstruct the nasal passages prevent drainage and aeration and favor the retention of infection should be removed Many of these patients need the thorough exenteration of the Caldwell Luc operation Often tissue studies of the removed membranes will show evidence of active infection in these cases complete surgery is usually a successful procedure It must be remembered that nasal surgery in these cases requires the utmost skill and completeness Many of the bad results attributed to nasal surgery especially in this category are due to incompetent and incomplete surgical technic (see Chap 17 and 27)

Vaccine therapy in the management of infectious factors in asthma is not a substitute for antibiotics or surgery when indicated The greatest usefulness of vaccines especially autogenous vaccines is in cases where the most complete surgery possible has been done but in the maze of tissue in the nasal passages and pharynx infection still persists

Climatologic management is helpful in many cases but disap

pointing in many others Experience indicates that it is not a substitute for usual management (Chap 28)

Finally it is important to reiterate that treatment of infectious factors in asthma to the neglect of proper elimination of hypersensitivity factors and immunization against them is most often the cause of disappointing results In the treatment of asthma there is no substitute for thoroughness in the complete management of the syndrome[8]

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21 | *Samuel J Prigal*

INFECTIOUS ASTHMA AND INTRAFAMILIAL CONTAGION

Most allergists agree that infection plays a role in asthma Cooke[1] has estimated that approximately 35 per cent of asthma cases are due to infection alone Chobot Uvitsky and Dundy in a study of 400 children found infection to be the sole cause of asthma in 30 per cent of the patients In 57 per cent of the cases both allergy and infection were implicated Therefore infection played some role in 87 per cent of the patients In a recent survey of 100 patients with asthma we found infection as the sole cause in 11 per cent allergy alone in 16 per cent and allergy plus infection in 73 per cent[3]

However there is no agreement among allergists as to the nature of the association between infection and asthma The varying explanations include bacterial allergy bronchospasm due to irritative or pharmacologic substances produced by microbial agents reflex spasm due to the inflammation per se acting as a foreign body modification of the patients sensitivity to allergens in the presence of infection (i e conversion of latent to active allergy) and the conversion of normal tissue by infection into modified proteins capable of sensitization In the authors opinion no single explanation is completely satisfactory or necessary It is conceivable that one or more of these mechanisms may be involved singly or in combination This aspect of the problem needs clarification Infection in allergic patients like all infections has a contagious aspect Therefore for several years the writer investigated families of asthmatic patients by bacteriologic methods in search of evidence of contagion

METHODS AND MATERIALS

The earlier studies of families were simple and arose out of the necessity of treating several patients in the same family simultaneously When cultures were taken from the nose throat or sputum it became apparent that there was a commonality of bacterial organisms in these patients which presumably was responsible for the infection Further questioning as to how these patients became infected led to a consideration of and search for a carrier within the household Originally only suspected members of the family were investigated These were selected on the basis of past history or evidence of current infection in the sinorespiratory apparatus Gradually the investigation was broadened to include all members of the family group and at times servants It was also found expedient to culture other sites of obvious infection (skin eye ear etc) presented by the patient or other members within the household As the search for methods of dissemination and spread of the infectious agent continued it was found necessary to study related families since many of their members also gave histories of chronic infections and much evidence of allergy There then arose the problem of specific identification of organisms Since we frequently found on culture the hemolytic staphylococcus which is so commonly encountered in normal asymptomatic individuals it was necessary to phage type this organism This new method of identification of the hemolytic staphylococcus is specific and has been of inestimable value in tracing the possible carriers and the mode of dissemination of the staphylococci[4]

RESULTS

Table 11 presents the findings observed in 82 families from 1949 through mid 1955 These comprised allergic patients in whom sinorespiratory infection played an important role

This table is an extension of studies presented previously[5] As will be noted cultures were obtained from 255 individuals of 77 families comprising the patients under treatment and members of their families Of these families 45 were studied completely with at least one culture from every member of the family The balance 32 families were incompletely studied Of the entire series of 77 families investigated bacteriologically 50 showed a commonality of one or more organisms suggestive of contagion

Since this report is primarily concerned with the relation of infection to asthma an analysis was made of the 49 asthmatic patients

TABLE 11 BACTERIOLOGIC EVIDENCE SUGGESTIVE OF CONTAGION IN 82 FAMILIES WITH SINORESPIRATORY INFECTIONS

Year	Number of families	Number of families studied by culture	Complete	Incomplete	Number of individuals studied by culture	Number of families showing possible contagion
1949	0	19	13	6	62	15
1950	14	12	7	5	41	8
1951	10	9	4	5	26	8
1952	12	11	2	9	35	4
1953	3	3	1	2	8	2
1954	15	15	12	3	54	8
1955	8	8	6	2	29	5
Total	82	7	45	32	255	50

and their families who were included in these studies It was noted that in six families there were two members of the family suffering from asthma in two families three members suffered from asthma and in one family there were four members with asthma Most of these patients had asthma of the mixed type due to allergy and infection

Of the 77 families studied by culture 49 included one or more members who suffered from asthma A summary of this special group is given in Table 12 It will be noted that of the 49 families studied 32 (65 3 per cent) showed bacteriologic organisms common to two or more members of the family and therefore suggestive of contagion Where the families were studied completely 81 2 per cent showed correlation (26 of 32) while the incompletely studied families showed only 18 7 per cent correlation (6 of 32)

The organisms cultured from those asthmatic patients in whose families there was evidence of contagion included the hemolytic staphylococcus isolated 19 times and hemolytic streptococci (all types) isolated six times Other organisms such as *Hemophilus influenzae Friedlander's* bacillus and *Proteus vulgaris* were too infrequently encountered to be adequately interpreted and on repeat cultures were often found to be transient Combinations of hemolytic staphylococci and streptococci were encountered seven times

To demonstrate the possibly contagious aspects of infectious asthma the studies of five families are briefly presented

TABLE 12 BACTERIOLOGIC STUDIES OF 49 FAMILIES WITH ASTHMA SUGGESTIVE OF CONTAGION

Number of individuals from whom cultures were taken	157
Number of families having one asthmatic patient	40
Number of families having two asthmatic patients	6
Number of families having three asthmatic patients	2
Number of families having four asthmatic patients	1
Number of families showing bacteriologic evidence suggestive of contagion	32 (65.3%)
Completely studied	26 (81.2%)
Incompletely studied	6 (18.7%)
Number of families showing the presence of the hemolytic staphylococcus in more than one member	19
Number of families showing the presence of the hemolytic streptococcus in more than one member	6
Number of families showing presence of combined hemolytic staphylococcus and streptococcus in more than one member	7

CASE REPORTS

Case 1 The A Family

This is a study of a single family Two brothers with asthma in whom infection played a role in association with allergy were seen in 1950 Antiallergic treatment alone had been unsuccessful Cultures revealed identical organisms in the upper respiratory tracts of both patients In view of frequent recurrences of upper respiratory infections and asthma intrafamilial contagion was suspected and the entire family was investigated bacteriologically

Figure 21–1 shows graphically the presence of hemolytic staphylococci and streptococci in the pharynx of all members of the family It also depicts for each member the incidence of past pyogenic infections presumably due to hemolytic staphylococci and/or streptococci which could serve as foci for reinfection The evidence points to the mother as possibly the prime carrier of the family Colonization of the family and reinfection of one member by another is a possibility indicated by the arrows (the heavier arrows indicate greater possibilities for cross infection)

Treatment of the infections (of both patients and other members of the family) hygienic measures to reduce cross infection and vaccine therapy along with antiallergic measures were most effective One of the boys has discontinued treatment and has had no asthma for two years despite marked sensitivity to pollens *Alternaria* and dust The other's asthma occurs infrequently during the pollen seasons while under treatment The incidence of respiratory infections within the family has been markedly reduced

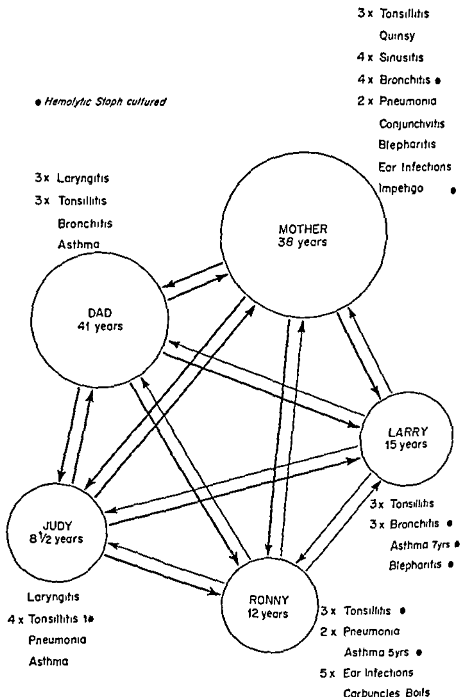


Fig 21 1 The A family

Case 2 The L Families

This is a bacteriologic study of a patient who had been subject to hay fever asthma and sinusitis and who gave a remarkable history of familial incidence of asthma respiratory infections and pyogenic infections of the eye or skin Cultures from the nose and throat were therefore taken from this patient and 24 members of the related L families

TABLE 13 THE L FAMILIES EPIDEMIOLOGIC AND BACTERIOLOGIC INVESTIGATION

Nathan L
Sarah S
AB

Children	Aaron L CTAE	Julius L CTBP	Leo L SBAE	Ernest L	Davis L CTSIA	□ Mildred L CTAS	Delia L T
Spouse	□ Ida	Pauline C	Paula CT	Rose S	Joseph B	Louis W	□ Albert Bo T
Grand children	Joan L Alice L IE	Dolores L Lenny L CBP	Irene L T □ Alfred L CTBE	Joseph L CA David L CA	Joy B B □ Gail B BTAE	□ Ross † C	□ Myrna Bo CTE Barbara Bo CTSIE □ Susan Bo CTS

Not investigated † Adopted son Died of cerebral accident 1 month after survey
□ Hemolytic strep Hemolytic staph

MEDICAL SURVEY

A—History of asthma with colds	7	E—History of eye infections	6
B—History of bronchitis	2	P—History of pneumonia or broncho-pneumonia	5
C—History of frequent colds (more than 2 per year)	15	S—History of sinusitis	7
		T—History of tonsillitis	13
		Tonsillectomies	14

BACTERIOLOGIC SURVEY

	L Families	"Normal" nonrelated families
Number of families	7	15
Total number of individuals	25	48
Number of hemolytic staph (pharynx)	15(60%)	8(16%)
Number of hemolytic strep (pharynx)	10(40%)	16(33%)
Number of organisms cultured	63	160

Table 13 shows the incidence of the various disease states encountered in the patient his progeny and the progenies of his six siblings For purposes of control 15 unrelated families not subject

chronic respiratory infections were also studied bacteriologically The incidence of hemolytic staphylococci was 60 per cent in the L families as compared with an incidence of 16 per cent in the control families The incidence of streptococci was practically identical in both groups (40 and 33 per cent respectively)

Subsequently an aunt of the patient (his mother s sister) was seen because of asthma of many years duration Again a hemolytic staphylococcus coagulase positive was encountered We had thus isolated hemolytic staphylococci in three generations Unfortunately phage typing of staphylococci was then unavailable to specifically identify the hemolytic

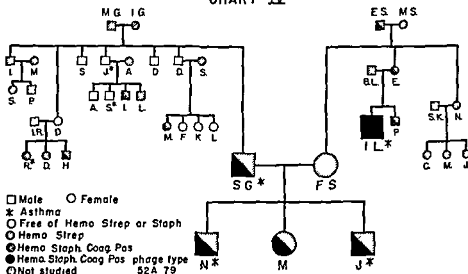


Fig 21 2 Bacteriologic studies of the G family and the related paternal and maternal families

staphylococci encountered in these related families Nevertheless the study was strongly suggestive of intrafamilial contagion and the possible passage of these organisms from generation to generation

Case 3 The G Family

Three members of the G family had asthma associated with respiratory infection Cultures from the nose and throat revealed hemolytic staphylococci coagulase positive identical in all three members as determined by phage typing Hemolytic streptococci were also present as were other organisms which did not however persist on subsequent culture Table 14 records the results of the cultures Note also that one parent (the father) has had innumerable pyogenic infections and that two of his three children developed asthma in the first year of life

Epidemiologic and bacteriologic studies of the family were made by exposing culture plates within the household and demonstrating the presence of hemolytic staphylococci (Type 52A 79) in the atmosphere. When the family planned to move to new quarters, plates were exposed in the empty new apartment, which had been freshly painted and cleaned.

TABLE 11 THE G FAMILY INCIDENCE OF INFECTIONS AND ASTHMA. BACTERIOLOGIC STUDIES SHOWING A HIGH INCIDENCE OF HEMOLYTIC STAPHYLOCOCCI IDENTICAL AS TO PHAGE TYPE, ALSO HIGH INCIDENCE OF ALPHA STREPTOCOCCI

Age	Allergic symptoms	Infections	Number of infections	Bacteriology—January 5, 19[illegible] Nose	Throat	Staphylococcus phage type
9 years	Asthma	Tonsilitis Sinusitis Bronchitis Styes Boils	4 5 4 2 2	Paracolon bacilli Alpha streptococci	*Staphylococcus aureus* (coagulase positive) Alpha streptococci	52A 79
9 years		Tonsilitis Ear infection	? 2	Gram negative bacilli (*Escherichia coli*) *Micrococcus tetragenous* Alpha streptococci	Alpha streptococci *Neisseria catarrhalis*	
8 years	Asthma	Tonsilitis	6	Alpha streptococci *Staphylococcus aureus* (coagulase positive)	Alpha streptococci *Staphylococcus aureus* (coagulase positive) *N catarrhalis* *Micrococcus tetragenus*	52A 79 52A 79
½ years		Tonsilitis Styes	10 [illegible]	Alpha streptococci *Staphylococcus aureus* (coagulase positive) Diptheroids *Bacillus subtilis*	Alpha streptococci *N catarrhalis*	52A 79
9 months	Asthma	Bronchitis	1	Alpha streptococci *Staphylococcus albus* (coagulase negative) *Staphylococcus citreus* *Bacillus subtilis*	Alpha streptococci *Staphylococcus aureus* (coagulase positive) Gram negative bacilli of *Escherichia* group	52A 79

and no staphylococci were encountered Three months after they moved into the apartment culture plates were again exposed and the hemolytic staphylococci (Type 52A 79) was again demonstrable in the atmosphere indicating that the G family brought not only their allergic environment but also their bacteriologic environment along with them

Suspecting intrafamilial contagion studies were also made of the six *siblings of Mr G and cultures were available from 13 of 22 members* of these families Hemolytic staphylococci which were coagulase positive were obtained in five members of these families but were dissimilar to the 52A 79 However a culture taken from another patient with pollen and infectious asthma a relative of Mrs G who had been successfully

TABLE 15 THE G FAMILY PERSISTENCE OF THE HEMOLYTIC STAPHYLOCOCCUS (PHAGE TYPE 52A 79) WITHIN THE FAMILY OBSERVED OVER A ONE YEAR PERIOD

	Patient— 9 months		Sibling— 5½ years		Father— (patient) 29 years		Patient— 8 years		Mother— 29 years	
Date	Nose	Throat	Nose	Throat	Nose	Throat	Nose	Throat	Nose	Throat
Dec 30 1954		52A 79	52A 79			52A 79	52A 79	52A 79		
Mar 14 1955			3A 44A							
Apr 12 1955			NT			52A 79		52A 79		
Apr 20 1955										
Jan 14 1956	42A 79		52A 79	44A				52A 79		52A 79

treated and discharged revealed the presence of hemolytic staphylococci Type 52A 79 Whether this former patient obtained this organism from the G family where he was a frequent visitor whether the transfer was the other way or whether the likeness was purely coincidental is conjectural Further check of Mrs G s siblings and their progeny did not disclose the same organisms so that there was no colonization in that part of the family by the hemolytic staphylococcus Type 52A 79 as there was with the G family Figure 21 2 shows the distribution of hemolytic staphylococci encountered in these studies

In order to determine the duration of the infection due to the hemolytic staphylococci Type 52A 79 cultures were taken of the G family at various intervals for over a year and these showed the persistence of this organism in the family particularly in the nose and throats of the three patients (Table 15) Thus it was not only demonstrated that the hemo

lytic staphylococci were absolutely identical as determined by phage typing but that they colonized the family and persisted for a long period of time

Treatment was directed primarily at the father who was presumably the prime carrier and all skin and eye infections wherever and whenever they occurred were actively treated with antibiotics The incidence of infections and asthma has been sharply decreased No attempts were made to skin test the children The father was treated with extracts of dust and pollen and a mixed catarrhal vaccine On several occasions when infections were present all three members of the family were treated simultaneously with aerosols using the closed chamber (bathroom) method described in Chapter 59

Case 4 The H Family

This is the study of a family in which the patient has intractable asthma and the husband suffers from chronic rhinopharyngitis The patient has been hospitalized on several occasions because of status asthmaticus All measures employed by several allergists had previously been unsuccessful Bacteriologic studies carried on at various intervals throughout an eighteen month period revealed the presence of identical hemolytic staphylococci in the respiratory tracts of the patient and husband and on

TABLE 16 THE H FAMILY THE OCCURRENCE DISTRIBUTION AND PHAGE TYPE OF HEMOLYTIC STAPHYLOCOCCI ISOLATED FROM THE PATIENT AND HER HUSBAND OBSERVED EIGHTEEN MONTHS

	Patient			Husband	
Date	Nose	Throat	Eye	Nose	Throat
July 21 1954	55 39		55 39		42E 70 42B
Oct 5 1954				42F 70	42E 70
Nov 19 1954	42E 70		42E 70 42B	42F 70 42B	
Feb 2 1955	42E 70 42B	NT	42E 70 42B	42F 70 42B	NT
Apr 19 1955	42F 70		42F 70	41A	
Jan 15 1956	41A		41A	41A	

the eyelids of the asthmatic patient who also exhibits chronic blepharitis As will be seen in Table 16 the identical staphylococcal organisms did not persist from the first to the last study Thus the patient demonstrated the first time a staphylococcus lysed by phages 55 and 39 but subsequently this changed to one lysed by 42 E 70 and this persisted On two occasions the patient became infected with the organism previously demonstrable in the throat of her husband It was noteworthy that at all times the same organism encountered in the respiratory tract of the patient was also found on her eyelids

The patient who previously could be comfortable only when given cortisone in large dosage is now doing well without steroids This followed simultaneous treatment with antibiotics of the infections about the eye and throat as well as the husband s rhinopharyngitis and reducing cross infection from the husband by active treatment of all colds and sore throats and the employment of hygienic measures

Case 5 The S' Family

The patient (Mr S) was asthmatic for many years the asthma resulting from specific allergies and from infections in the respiratory tract At times the asthma was severe and hospitalization was necessary Invariably it was relieved by antibiotic therapy but this relief was usually of short duration Cultures from the nose and throat had been taken many times and almost invariably showed the presence of a combination of hemolytic staphylococci and streptococci Table 17 charts the organisms encountered over a two year period and their sensitivities to in vitro inhibition testing with the antibiotics then in use It is noteworthy that following the use of each antibiotic that was selected on the basis of sensitivity studies—penicillin bacitracin streptomycin aureomycin and terramycin—the organisms developed resistance to that antibiotic In view of recurrent infections in the sinorespiratory apparatus despite repeated antibiotic therapy a search for possible carriers was made and it was disclosed that both wife and daughter had hemolytic streptococci and staphylococci in their noses and throats Neither of them were subject to unusual respiratory infections

The treatment was never truly effective in this patient despite suggestions for improving hygiene the use of multiple antibiotics in combination and vaccine therapy Recurrent tonsillitis and sinusitis invariably followed by asthma continues to plague the patient

COMMENT

The role of intrafamilial contagion in repeated or chronic respiratory infection has been investigated by Prigal [5] Finke [6] and Dingle [7] In the author s studies the hemolytic staphylococcus has frequently been implicated [3, 8–10] This raises the question of pathogenicity since this organism may be normally encountered in about 60 per cent of the population in the nose throat skin or stool [11] That the staphylococcus can be pathogenic is attested to by the severe and often *fatal infections due to this organism Where a hemolytic staph*ylococcus shows a positive coagulase reaction it is considered more apt to produce disease than when not showing either the hemolytic or the coagulase reactions [1]

The most logical explanation for occurrence of disease presumably due to the hemolytic staphylococcus is to postulate the exist

ence of a latent subclinical infection which periodically becomes active either due to the stimulation of viruses as in the common cold or by the reduction of the patient s defense mechanisms as a

TABLE 17 THE S FAMILY CLINICAL DEVELOPMENT OF RESISTANCE TO FIVE ANTIBIOTICS EMPLOYED IN SEQUENCE TO ERADICATE INFECTION DUE TO PERSISTENT INFECTION WITH HEMOLYTIC STAPHYLOCOCCI AND HEMOLYTIC STREPTOCOCCI

Date	Organisms cultured	Antibiotic previously employed	Sensitivity tests Penicillin	Bacitracin	Streptomycin	Aureomycin	Terramycin
Jan 20 1949	Hemolytic streptococci	Penicillin	−	±	−	0	0
	Staphylococci		−	+	+	0	0
Feb 3 1949	Streptococci	Bacitracin	+	+	+	0	0
	Staphylococci		±	+	−	0	0
Feb 1 1949	Streptococci	Penicillin and	+	+	−	0	0
	Staphylococci	bacitracin	+	±	−	0	0
Mar 8 1949	Hemolytic streptococci	(Hospitalized)	−	±	±	±	0
	Hemolytic staphylococci	Large doses of penicillin	−	−	±	±	0
Oct 5 1950	Hemolytic streptococci	Aureomycin	−	±	−	−	+
	Hemolytic staphylococci		−	±	−	−	+
Feb 19 1951	Hemolytic streptococci	Terramycin	−	−	−	−	−
	Hemolytic staphylococci		+	−	±	−	−

Identical organisms were isolated from pharyngeal cultures of wife and daughter in whom there was no clinical evidence of infection

result of illness vitamin depletion modification of antibody production endocrine disturbances or other stresses In this the staphylococcus resembles the tubercle bacillus Presumably infection with

the staphylococcus can occur early in life and continue for some time perhaps for a lifetime in some cases although this needs verification We do know that blepharitis or chronic otitis media due to a staphylococcus infection may persist for many years resisting all types of treatment This is also true for staphylococcal osteomyelitis as is illustrated by the following experience related by Dr John Blair of the Hospital for Joint Diseases In 1941 a boy of seven was admitted because of acute osteomyelitis verified by x ray and by a positive blood culture in which a hemolytic staphylococcus was harvested This organism was saved The patient was successfully treated with a staphylococcal antitoxin sulfathiazole and blood transfusions and without surgical intervention In 1942 the patient was readmitted with osteomyelitis at the same site in which a draining sinus was present and from which a hemolytic staphylococcus was also cultured and saved After surgery (saucerization) there was complete recovery In December 1954 the patient returned with osteomyelitis again at the same site and for the third time a hemolytic staphylococcus was cultured Since phage typing was then available all three organisms were typed and proved to be identical Here then was infection due to the same organism encountered over a period of thirteen years with a latent period of twelve years duration

With our present knowledge of the staphylococcus its remarkable adaptability to all kinds of changes of the environment including development of resistance to antibiotics its relative failure to stimulate production of antibodies and its destructive action on white blood cells we can understand the reasons for the persistence of infection due to this ubiquitous hardy and highly versatile organism The role of the staphylococcus and the problem it creates for the allergist has already been reviewed in greater detail [13]

Persistence of infection with the staphylococcus may be due to another mechanism namely reinfection [10] This may come from sites of neglected low grade chronic infection in the patient s skin eye or ear or members of the family may act as carriers either because of obvious infections or because of latent infection diagnosed only by culture

Although this study concerns itself primarily with contagion within the family group (where chronic infections already exist in a parent and are likely to occur in the children) [6, 7] it is understandable that infection may also occur from extrafamilial sources This is particularly true of viral infections such as measles mumps and chickenpox Finke [6] has shown however that for respiratory infec

tion of bacterial origin there is usually a history of onset in the first few months or years of life prior to the school age This is particularly true where there is a family tendency to chronic respiratory infection

The occurrence of asthma in patients with respiratory infection seems to be predicated in most patients in these studies on a combination of an underlying allergic state and a superimposed infection There are patients however in whom there is no demonstrable or overt allergy but in whom chronic infection may produce bacterial sensitization causing asthma

There are probably other roles that infection plays in the production of asthma We have encountered instances of asthma due solely to infection without any demonstrable evidence of sensitization bacterial or otherwise Here any attempt at explanation is at this time purely speculative

It is certain however that infection does play an important role in asthma and to treat this problem properly the etiologic agent should be identified and the proper antibiotics employed (In our own experience a combination of antibiotics such as neomycin polymyxin or aerosporin and bacitracin administered as an aerosol is highly effective because of its broad spectrum of activity local topical action and nonsensitization) Equally as important as specific therapy directed against the infection is the employment of public health measures to prevent reinfection It is certainly a fallacy to remove a focus of infection —say the tonsils—without simultaneously treating an existing chronic conjunctivitis or blepharitis in the patient or in carriers within the household The author has successfully treated asthmatic children by controlling the infection of their parents or siblings In one instance success was achieved only after treating a grandfather with chronic sinusitis with whom the patient lived Repeated culture of each member of the household had revealed him to be the only member of the family to harbor a hemolytic staphylococcus presumably identical with the one repeatedly encountered in the grandson Since the death of the grandfather several years ago there have been few respiratory infections and no asthma Previous treatment in a well recognized allergy clinic which was limited to antiallergic therapy removal of tonsils and adenoids irradiation of pharyngial lymphoid tissue and the occasional employment of antibiotics had been unsuccessful

Eradication of chronic infections in the patient or in familial contacts is desirable but not always achievable where the hemolytic staphylococcus is involved Therefore it is important to improve the

immunity of the patient as well This may possibly be achieved passively and temporarily by injections of gamma globulin or actively by the use of vaccines preferably autogenous

That there are shortcomings in this type of investigation is acknowledged The methods of culture were limited to accessible surfaces Infections in the sinuses or bronchi or deep within their membranes may have been overlooked No irrigation of the sinuses or bronchoscopy was performed in any of these patients since most of them responded to aerosol therapy with antibiotics Furthermore the use of a single medium for culture as well as single sites of culture and a single swab for most patients (although some were cultured repeatedly over long intervals of time) is fraught with error

Additional errors undoubtedly occurred in this study of infection since it was strictly a bacteriologic investigation The role of viruses in acute respiratory infections is only now beginning to be studied by Huebner and his group [14] There are many viruses already listed in the APC (adenoidal pharyngeal-conjunctival) group and many more to be identified Unexplained as yet is the possible role of the viruses in *chronic* respiratory infections That viruses can remain latent over long periods of time is attested to by the occurrence of infection with the virus of herpes simplex This virus may be dormant for many years only to be converted from latent to active infection by strong sunlight or by debility due to infection as in pneumonia Huebner has also shown that some of the APC viruses may persist in adenoid tissue for a long time becoming recoverable only when the dying tissue releases the viruses

Finally in evaluating this study the author is only too well aware that simple identification of similar organisms even to the point of identical phage type does not actually prove infection and contagion This may merely be coincidental since the hemolytic staphylococcus and streptococcus are so ubiquitous The evidence however is strongly suggestive of infection and contagion by the staphylococcus in view of the nature of the organism its persistence and its ready conversion from latent to active infection

An interesting by product of this investigation is the challenge it offers to the commonly accepted role of heredity in the etiology of asthma Since this role is based largely on family studies and since this investigation shows that asthma may at times be related to intrafamilial infection and contagion one wonders about the true role of heredity While this study does not disprove the possible role of heredity it diminishes it To the criticisms of the heredity role presented by Ratner and Silberman [1] in which they point to flaws in the early family studies may now be added the failure to consider

the bacteriologic environment of an illness so frequently associated with infection Apropos it may be recalled that prior to the discovery of the tubercle bacillus tuberculosis was considered a hereditary disease obviously because it occurred in families Since we have strong evidence for the role of heredity in hay fever where no infection is involved we can assume that heredity does play a role in the related disease asthma The question is how much heredity and how much intrafamilial infection are involved

Similarly questions can now be raised about psychologic reasons for the reported relief of children when they are separated from their families and sent to institutions for asthmatic children or away from home for a change in climate Is the relief in any way related to a change in the bacteriologic environment?

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Harry H Shilkret

OCCUPATIONAL ASTHMA

The importance of bronchial asthma as a health problem in various industries has long been recognized[1,3] The incidence of bronchial asthma in industries according to Spain and Fontana[1] is the same as in the general population about 5 per cent

To differentiate between occupational and nonoccupational asthma a thorough occupational history is of great assistance This includes information on the date of onset of the complaints whether or not the asthmatic condition existed prior to the time the claimant was exposed to a particular substance whether the attacks occur usually at work and whether they disappear entirely while the patient is away from his work

The symptoms in occupational asthma are not characteristic They are identical with those of nonindustrial asthma Particular attention should be given however to the origin of the symptom in relation to exposure to occupational allergens It is only when this has been ascertained that a distinction can be made between symptoms which are due to nonoccupational diseases and those which are occupational since both may exist in the same patient

As in other allergic diseases occupational asthma rarely develops after an initial contact with an offending allergen Usually there is a sensitization period of months or even years before any allergic manifestations appear This has been the experience of the author in reviewing over 200 case histories of patients claiming compensation for asthma

The clinical investigation should include roentgenologic and elec

trocardiographic examinations and a thorough work up including skin testing Patch tests and ophthalmic and inhalation tests are used as indicated and are frequently found to be informative if there are intelligent appraisal and proper interpretation of the data Positive reactions should be correlated with the occupational environment

Bronchial asthma occurs in people working in various types of industry most frequently in bakers furriers barbers beauticians and hat makers The Department of Labor lists over 100 occupations in which asthma occurs[4] Most cases of occupational asthma are due to inhalants organic and inorganic (mineral) dusts fumes and vapors Occasionally ingestants play a role and asthma may occur in wine tea and coffee testers Contactants are frequently the cause of occupational dermatoses which usually precede the onset of the asthmatic state in furriers and bakers

Bakers come into close contact with flour by inhalation and those with bronchial asthma usually show a marked sensitivity on skin testing to one or more of the extracts of cereals (wheat rye buck wheat and corn) Linko[2] found that 66 of 328 workers in bread factories gave clinical evidence of being sensitive to wheat flour Of these 40 had coryza 20 had coryza and asthma and 6 had asthma alone—that is 26 or 7 9 per cent of all the workers had asthma either alone or in association with coryza

The substances which are commonly the cause of asthma among those engaged in the fur industry are animal danders and fur dyes Other agents less often responsible are dusts and fumes physical agents such as extreme heat or cold and chemical substances other than dyes which are employed in the preparation and dyeing processes

Walzer and Pine[5] in an excellent article Hypersensitiveness in the Fur Trade state that dander rather than the hair of the animal is the excitant Among the animal inhalants rabbit epithelium is the most frequent offender Animal skins and hairs which have been preserved treated and dyed may lose some of their excitant prop erties as a result of these physical and chemical processes

The dye most commonly used in the fur industry is paraphen ylenediamine and its oxidation products (quinone diamine) Hyper sensitiveness to dyes is tested for by means of patch tests since sensitivity to chemical substances is not as a rule determinable by the scratch intracutaneous or passive transfer tests The results of these tests are read forty eight to seventy two hours later Positive reactions are significant negative reactions do not eliminate the testing agent as a cause since the method of testing (patch) is a poor one for inhalant sensitivity

Shilkret and Swartz[3] skin tested 100 allergic individuals within and outside of the fur industry with extracts of fur factory dusts containing dyes They found the percentage of positive reaction in this group to be approximately the same (30 to 40 per cent) In comparison the positive reactions to common house dust in each group varied between 10 and 57 per cent They concluded that a positive reaction to factory dusts is of no greater significance for etiology of symptoms than a similar reaction to other allergens and that more evidence than a positive skin test is necessary to implicate these dusts in a causal relationship with presenting symptoms

Dye and dander sensitivity is preventable to a great extent Work in the fur dyeing industry is contraindicated for the atopic individual Preemployment examinations by experienced industrial physicians should cut down considerably the incidence of asthma in industry

Every step should be taken to avoid unnecessary exposure to dyes in order to prevent the development of sensitivity Well ventilated rooms the cooking of dyes under a hood with a strong draft and the wearing of rubber gloves and a mask by the worker engaged in the cooking are precautionary measures which may do much to diminish the hazards encountered in the fur dyeing industry

The most common causes of the allergic respiratory responses of beauty parlor workers are the powders and rouges that contain ground orris root or rice powders the henna of hair dyes quince seed oil and the gums tragacanth and karaya Where orris or rice powder is the eliciting agent a satisfactory degree of immunity may be achieved by specific injection therapy as described in Chap 56

Hat makers may become sensitive to the material used in the making of felt especially the rabbit dander The bleaching agents such as banana oil and oxalic acid are also secondary offending agents in this occupation Protection can rarely be obtained by specific (hyposensitization) therapy The lack of success is due usually to the overwhelming exposure and the frequency of systemic reactions following treatment

Occupational asthma usually associated with upper respiratory allergies is found also in the bedding and furniture manufacturing industries where workers come in contact with various types of organic dusts e g animal danders (horse goat cow rabbit etc) feathers and the by products of cotton kapok flaxseed glue and wood dusts In the food processing and food distributing industries canners warehouse workers and grocers may be affected by the many occupational dusts fumes and vapors that emanate from such products as coffee tea cocoa spices and cereals Veterinarians farm

ers pet shop workers salesmen of dog and cat food and handlers of laboratory animals may have asthma from close contact with various animals Farmers foresters tree surgeons nurserymen florists and gardeners are necessarily exposed to plants which are responsible for occupational allergies Brewers and salesmen handling hops are at times rendered asthmatic by these substances

As in other respiratory types of allergy in which the allergens are air borne positive skin reactions are usually obtained when the causative agent of the occupational allergy is a protein substance Chemicals and drugs and other haptens may be the excitant agents of bronchial asthma and allergic rhinitis These substances rarely produce positive skin reactions by either the direct or the indirect method of testing (passive transfer) Such tests made with a chemical or a drug are not without danger in an allergic individual since the risk of systemic reactions is always present (see Chap 16)

The diagnostic skin testing procedures scratch or intradermal should *be employed to verify the allergenicity of substances* suspected because of the history and to search for undetermined causes Extracts of factory dusts have special usefulness in the testing of patients with asthma in whom an occupational cause is suspected To avoid undue reactions from these extracts it is advisable to scratch test first and follow later with the intracutaneous test if the former test proves negative

Therapeutically as with nonoccupational asthma the first and most important step is to break the contact between the patient and the offending substance If complete avoidance of the air borne allergens in the occupational environment cannot be effected a protective mask may be worn over the nose and mouth although many consider it uncomfortable and inconvenient Industry has become well aware of occupational asthma as shown by its efforts to supply improved ventilation isolate or prevent dusty processes install air conditioning and exhaust systems and improve its plans and designs for plant and factory structures Wet methods of work are often practical in minimizing the effects of exposure to factory dusts

Where elimination of the specific allergen or avoidance of contact is incomplete or cannot be satisfactorily achieved methods of immunization (hyposensitization therapy) may be attempted Unfortunately owing to the continued exposure of the patient who is closely confined in a shop or factory results of this procedure are often poor In dye sensitive individuals attempted desensitization is unsuccessful and most often harmful These patients are advised to give up their occupations and to seek employment where the offending substances are not present in the environment

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Paul F deGara

23

DIFFERENTIAL DIAGNOSIS OF ASTHMA

All that wheezes is not Asthma—Chevalier Jackson

Wheezing paroxysmal expiratory dyspnea and cough are typical symptoms of allergic asthma However from a differential diagnostic viewpoint certain other conditions which may be accompanied by similar symptoms must be ruled out The most important diseases which may be confused with true allergic asthma may be classified into the following groups (1) mechanical conditions (2) infections and inflammatory conditions (3) cardiac and circulatory conditions and (4) miscellaneous conditions

As a rule allergic asthma can be diagnosed correctly on the basis of an accurate history a complete physical examination and a few laboratory studies The latter should always include radiographic examination of the chest total and differential leukocyte counts examinations of nasal smears and sputum and skin tests While roentgen examination of the chest may not reveal abnormal findings in uncomplicated asthma nevertheless it is invaluable for the diagnosis of the complications of asthma (emphysema bronchiectasis and others) and in differentiating true allergic asthma from some conditions resembling it The total number of leukocytes is usually normal in asthma but the differential count shows an increase in eosinophils (eosinophilia) averaging 4 to 8 per cent but occasionally reaching as high as 50 per cent The eosinophilia is especially marked at the end of an asthmatic seizure Frequently smears from nasal secretions in allergic asthmatics also contain eosinophilic cells (10 per cent or more) The sputum in asthma is mucoid and colorless

(or grayish white) if there are no complications With secondary infections it may become mucopurulent and the color may change to greenish or yellowish or be blood tinged Furthermore the sputum may contain small round granules which are visible to the naked eye (Laennec s perles) When it is viewed against a dark background one may also notice mucous threads 5 mm to 2 cm in length (Curschmann s spirals) On microscopic examination hexagonal pyramids (Charcot Leyden crystals) and eosinophilic cells are frequently detectable

Positive skin tests are of considerable significance in the diagnosis of asthma especially if they can be correlated with the clinical symptoms

In some instances additional investigations will be required These may include radiographic examinations of the paranasal sinuses pulmonary function studies bacteriologic cultures bronchoscopy biopsies determination of the circulation time electrocardiograms and other studies

MECHANICAL CONDITIONS SIMULATING ASTHMA

Any type of obstruction to respiration may produce symptoms suggestive of asthma

Foreign Bodies Particularly in children the possibility of a foreign body producing dyspnea should always be kept in mind Usually there is a history of sudden onset of nonspasmodic shortness of breath which is not relieved by ephedrine or epinephrine In allergic asthma the dyspnea is paroxysmal in character and usually responds promptly to these drugs Frequently the physical signs are noted only on the side obstructed by the foreign body e g an aspirated peanut a tooth broken off from a denture Roentgenograms may be useful but if the object is translucent bronchoscopy must be performed to establish the diagnosis

Enlargement of the Thymus In this condition symptoms simulating asthma in infancy are caused by compression of the trachea or of a bronchus The diagnosis can be made with the help of roentgenographic examinations

Substernal Thyroid Radiographic studies are required to differentiate asthma like symptoms produced by substernal thyroid from true allergic asthma

Neoplasms of the Lung Both primary and metastatic tumors may press on the airways and produce wheezing and dyspnea Similarly mechanical factors operate through pressure from enlarged lymph nodes in lymphosarcoma leukemia and Hodgkin s disease The

physical examination implemented by hematologic radiographic and bronchoscopic studies possibly with biopsy will establish the diagnoses in these conditions

Aneurysm of the Thoracic Aorta This is another cause of obstruction from without the bronchial tree apt to produce a picture resembling asthma The correct diagnosis can be arrived at without great difficulty as a rule

Thoracic Deformities Dyspnea may be experienced by patients with chest deformities which interfere with the normal respiratory excursions of the lungs

Other Conditions Finally shortness of breath may occur as a result of pressure originating below the diaphragm as in pregnancy or with ascites

INFECTIONS AND INFLAMMATORY CONDITIONS SIMULATING ASTHMA

Asthmatic Bronchitis (or Bronchitic Asthma) This is a clinical entity usually labeled chronic bronchitis with symptoms resembling asthma *It may occur in childhood although it is essentially* a disease of adults over forty years of age (The reader is referred to Chap 21 for greater detail and for the differentiation between the various lung diseases associated with asthma)

Tuberculosis Asthma and tuberculosis may coexist in the same *patient although this is not common (tuberculosis apparently occurs less frequently in asthmatic individuals than in nonasthmatics)* Since the symptoms of asthma may mask a tuberculous process there is a danger that tuberculosis will be overlooked in the asthmatic patient This can be avoided by carefully observing every patient with asthma for signs of tuberculosis and if it is suspected making chest roentgenograms at regular intervals along with sputum examinations for the presence of tubercle bacilli The tuberculin tests should also be performed

Pneumoconiosis (Miners Asthma) and Pneumonitis In both these conditions there is wheezing and dyspnea which is nonspasmodic and is thus differentiated from the spasmodic shortness of *breath typical in allergic asthma In addition ephedrine and epinephrine* are of little value in pneumoconiosis and in pneumonitis X ray examination is helpful diagnostically

CARDIAC AND CIRCULATORY CONDITIONS SIMULATING ASTHMA

Cardiac Asthma Since cardiac asthma also causes paroxysmal dyspnea and wheezing it resembles true allergic asthma more closely

than other conditions Cardiac asthma has its onset usually in middle age It is due to organic heart disease and occurs in hypertensive patients with sudden left ventricular failure pulmonary hypertension secondary pulmonary emphysema and pulmonary edema Diseases of the coronary vessels (sclerosis and occlusion) also may cause the clinical picture of cardiac asthma It occurs mostly during the night Further discussion of this subject is presented in Chap 25

Cardiac Dyspnea This occurs in connection with mild cardiac decompensation as contrasted with the paroxysmal nocturnal dyspnea (cardiac asthma) due to acute cardiac failure Since cardiac dyspnea is continuous and nonparoxysmal and since there is no wheezing and no prolongation of the expiratory phase the differentiation from allergic asthma should not present difficulties

Periarteritis Nodosa Dyspnea resembling that of asthma may occur if periarteritis nodosa involves the pulmonary vessels Other clinical manifestations of this disease as well as hematologic findings and biopsy studies will differentiate it from allergic asthma

MISCELLANEOUS CONDITIONS SIMULATING ASTHMA

Psychosomatic Conditions Psychosomatic conditions may simulate asthma Before labeling the condition psychogenic it is essential to conduct a thorough allergic investigation in the patient If sensitivities can be detected they should be treated according to the usual methods of avoidance and desensitization In many asthmatic patients with psychodynamic overtones no special psychiatric therapy is needed but in some cases psychotherapy may be necessary in addition to antiallergic management Some asthmatics have been labeled hysterical psychoneurotic or malingerers until skin tests indicated allergic sensitivity In a recent experience skin testing revealed sensitivity to a dog present in the patient s surroundings Elimination of this offending allergen was followed by a miraculous cure which was not achieved by other therapeutic procedures including prolonged psychotherapy One must of course remember that a psychosomatic component may be present at one time or another in many patients with asthma Proper management of the asthmatic patient must therefore consider the somatic as well as the psychic aspects of the disease (see Chap 8)

Sighing Dyspnea This occurs in emotionally disturbed patients and may be mistaken for asthma which it resembles only in the complaint of dyspnea The absence of wheezing and the prolonged expiratory phase serve to differentiate the two conditions which may rarely be confused with allergic dyspnea

Toxemia Dyspnea in connection with toxemia may occur but this is also rarely mistaken for asthma

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Rubin Grossman and Samuel J Prigal

!ONCHITIS, EMPHYSEMA, AND [HER PULMONARY DISEASES IN :LATION TO ASTHMA

Bronchitis emphysema and asthma are distinct clinical entities uch may exist independently More often however there is an :errelationship particularly among asthma bronchitis and em ysema It is the purpose of this chapter to examine this relation ip to offer criteria for the differential diagnosis of these condi ons and to suggest the type of therapy indicated We also intend review the relationship of asthma to such pulmonary diseases as onchiectasis atelectasis and bronchostenosis

In the patient with chronic asthma particularly where infection ays a predominant role it is not unusual to find asthma bron itis and emphysema coexisting simultaneously The relationship tween these three states is dynamic A patient may begin with rely allergic asthma the consequence of specific extrinsic allergy d if improperly or inadequately treated develop chronic bron itis then as this state persists proceed into chronic obstructive ılmonary emphysema On the other hand a patient may begin th chronic bronchitis and after many years of this condition velop so-called intrinsic bronchial asthma (without any ap rent allergic background or known etiology) This combination ay subsequently and imperceptibly blend into chronic obstructive nphysema In either case the end result is the same Emphysema es not per se initiate the chain of events portrayed it is commonly

accompanied by chronic bronchitis but it would be difficult if not impossible to indicate which initiates and which follows

In order to understand better the interrelationships of asthma bronchitis and emphysema and the role each plays in producing symptoms it is expedient to consider each of these as isolated disease states

EMPHYSEMA

Obstructive pulmonary emphysema may be regarded as a connective tissue degenerative process which results from loss of elastic tissue and thinning attenuation and finally rupture of the alveolar walls This process commonly results in thin walled cysts of varying size creating blebs and bullae The cysts are more numerous in the apex and the periphery of the lungs but may not be grossly evident Mucosal thickening and submucosal inflammatory changes in the terminal bronchioles are also frequently observed These lesions occur diffusely throughout both lungs with varying severity and may be accompanied by varying degrees of diffuse pulmonary fibrosis chronic bronchitis pneumonitis and/or localized bronchial lesions The morphologic picture in emphysema may resemble that of severe intractable asthma There is plugging of the bronchioles and smaller bronchi with inspissated mucus Microscopically there may be noted patches of pneumonitis hypertrophied smooth muscle of the bronchioles hyperplasia of the mucus secreting glands of the smaller bronchi and diffuse infiltration of eosinophils neutrophils and monocytes

There are functional counterparts to these structural changes Expiratory obstruction increases expiratory work especially with increased ventilation on exercise resulting in exertional dyspnea This change in the character of expiration is evidenced by spirograms and by measurement of the maximum breathing capacity Associated with the structural changes are areas of alveolar underventilation and an increase in the residual capacity at the expense of the vital capacity More significantly the functional residual capacity is increased (see Chap 14 Pulmonary Function Tests) Circulatory changes appearing late in the disease are a reduction in the pulmonary vascular bed and a decrease in the diffusing capacity (alveolar capillary) of the lung due to a reduction in the total diffusing surface These changes contribute to hypoxemia especially on exercise and hypercapnea may occur in the most advanced cases The increased resistance in the pulmonary vascular bed increases the work of the right ventricle and this may eventually lead to right heart failure (cor pulmonale)

The functioning lung in the intact body represents a viscoelastic system which is ventilated by muscles and controlled by reflexes mediated by the circulating blood and the nervous system The elastic properties of the lungs and the thoracic wall principally determine the amount of air in the lungs in the resting position either inspiratory or expiratory In addition to the tendency of the elastic structures to return to the normal resting position viscous properties of the pulmonary parenchyma as well as resistance to air flow influence inspiratory and expiratory changes The viscoelastic properties of the lungs have been shown to be altered in pulmonary emphysema so that the resting lung contains a greater volume of air than normal suggesting a decrease in the elastic forces tending to deflate the lungs The slowing of gas movement principally during expiration which characteristically increases as the lung deflates may become a total obstruction with rapid forceful expiratory effort An attempt to ventilate the lung maximally causes an initial decrease in the expiratory flow as related to the inspiratory flow resulting in a marked decrease in the maximal breathing capacity with characteristic trapping of air in the lungs The exact method by which expiratory obstruction develops remains in doubt

More than a century ago Laennec[1] postulated that expiratory obstruction was due to mucous secretions A more recent concept attributes the slowing expiration to the collapse of the bronchioles and small bronchi due to the loss of surrounding pulmonary parenchyma which ordinarily exerts an elastic pull in all directions and maintains the patency of the bronchiolar lumens It is conceivable that with rupture of the alveolar walls and loss of elastic tissue the spring holding open the small air passages is reduced allowing their collapse during a forced expiratory effort This theory postulates an intimate relationship of expiratory obstruction to alteration of the viscoelastic properties of the lungs It suggests the possibility of an unphysiologic vicious cycle perpetuating the functional and anatomical changes

Another possible explanation for emphysema is one involving partial obstruction due to check valve mechanism This was recently reemphasized by Lister[3] who also feels that asthma is the disease state which provides such a mechanism and is therefore the sole precursor of generalized emphysema

Exertional dyspnea is the primary and almost invariable complaint in emphysema It is questionable whether a diagnosis of pulmonary emphysema can be made in the absence of dyspnea In some cases this is the only complaint Although a classic insidious onset of dyspnea is most often described by patients some will re

member the time and circumstances of the first appearance of this symptom Usually an attack of flu or pneumonia causes dyspnea which never thereafter quite disappears A severe or unusual effort such as pushing a car or shoveling snow may bring the patient to a sudden realization that he has diminished exercise tolerance Once dyspnea is first noted it usually progresses slowly often being present for years before medical advice is sought

Chronic or recurrent cough is another almost universal complaint Usually there is at least intermittent production of sputum which is either mucoid or mucopurulent Occasionally hemoptysis occurs which may or may not be associated with chronic bronchiectasis or chronic bronchitis Wheezing which is the most obvious clinical sign of expiratory obstruction is another complaint The wheezing of emphysema may resemble asthmatic wheezing but usually is much less pronounced and is nonseasonal except for aggravation on exposure to cold wind or dust The wheezing and dyspnea though present the year round and somewhat worse in the winter may have a marked day-by-day variation The symptoms are not always related to weather changes and are usually most noticeable in the morning on arising

The clinical appearance of the patient with advanced pulmonary emphysema is fairly characteristic The facial expression may be anxious and the accessory muscles of respiration in the neck usually contract in an effort to elevate the thorax during inspiration Simultaneously the abdomen may be retracted in a paradoxical fashion further demonstrating the inefficient uncoordinated work of the musculoskeletal system The veins of the neck may become prominent during expiration which may be forced with grunting and an audible wheeze The patient may speak in short jerky phrases The expansion of the chest is usually limited to less than 1 in but is often within normal limits ranging up to 2½ in The more significant limited motion of the diaphragm may be demonstrated on percussion or noted during fluoroscopic examination of the thorax

It is often difficult to make a diagnosis of emphysema on the basis of a routine roentgenogram of the thorax However inspiratory and expiratory roentgenograms of the thorax will increase the accuracy of diagnosis Pulmonary function tests of ventilation though not helpful in differentiating emphysema from asthma nevertheless may indicate the degree and type of ventilatory insufficiency (restrictive or obstructive) This information may be useful in the prognosis and treatment of these related conditions

A barrel type of chest is frequently misleading as a sign of em

physema Many cases of emphysema in the early stages are not associated with a barrel chest and conversely many elderly men with dorsal kyphosis and a barrel chest do not have emphysema

Pulmonary osteoarthropathy is conspicuously absent in emphysema The skin is more pallid than one would expect on the basis of the hemoglobin content of the blood If secondary polycythemia is pronounced there may be plethora and cyanosis Expiratory rhonchi though obscure during normal breathing may be demonstrated by *having the patient breathe rapidly Diminished intensity of heart* sounds and reduction of the area of cardiac dullness may also be noticed The physical signs are variable from patient to patient and may not be observed unless carefully looked for

CHRONIC BRONCHITIS

Chronic bronchitis[4] is a long standing disease of the tracheo bronchial tree with chronic inflammatory fibrotic and atrophic changes in the mucous membrane and deeper bronchial structures frequently associated with pulmonary fibrosis emphysema or other chronic pulmonary disease It is associated with low grade infection inadequate pulmonary drainage[5] mechanical distortions inadequate circulation and tissue malnutrition leading to both atrophy and connective tissue replacement Since chronic bronchitis is usually a secondary condition one must search for the primary disease The best approach is by differential diagnosis based on a meticulous his tory and physical examination Special laboratory study of care fully collected sputum may give a clue to the diagnosis If the phys ical findings are unilateral one must think of a foreign body or a tumor

The primary complaint of the patient with chronic bronchitis is cough of varying severity At times because of infection or because of irritation the cough may be severe enough to produce momentary unconsciousness More often the cough is mild and may be attributed by *the patient to smoking especially as some patients may cough* only when smoking or when in a smoky atmosphere The cough most often results from simple irritation infrequently from allergy to tobacco

Less often the patient complains of dyspnea hemoptysis or puru lent expectoration When these occur other possible complications must be considered such as bronchiectasis and emphysema Most patients ignore the cough and do not seek medical attention until dyspnea or hemoptysis ensue A history of episodes of acute bron

chitis often beginning in infancy or early childhood is usually obtained The history may also reveal frequent infectious insults to the lungs such as pneumonia or bronchopneumonia Later in life there may also be episodes of right heart failure but this is usually due to cor pulmonale following advanced emphysema

Bronchitis may result from exposure to such varied agents as irritating tobacco smoke irritating dusts such as silica or iron allergenic dusts such as flour fur or dyes and irritating fumes or volatile chemicals found in many industries and in smogs Purely allergic reactions in the bronchi without secondary spasm and frank asthma are possible but has not been conclusively demonstrated

Colmes and Rackemann[6] and Prigal[7] have described allergic cough which is presumably a reaction involving the trachea and possibly bronchi without other signs of asthma such as dyspnea or wheezing There is no doubt that coughing purely on an allergic basis exists One can induce this by an overdose of specific allergens There is no proof however that allergic reactions are so localized without producing frank asthma Allergic cough is usually the forerunner of asthma as Colmes and Rackemann first indicated In view of the lack of evidence for its localization we should not consider allergic cough as a disease entity but rather as an allergic symptom Whether this is truly allergic bronchitis or allergic tracheitis as Kahn[8] considers it to be awaits demonstration

In the examination of the patient with pure bronchitis the physician may find little except for inspiratory rales scattered throughout the chest Rales limited to the bases should indicate a thorough cardiac examination As a rule the laboratory and x ray findings are unrevealing When there is a leukocytosis or when the sedimentation rate is high some parenchymal involvement should be suspected or some infection elsewhere such as sinusitis should be searched for Chronic sinusitis is frequently associated with chronic bronchitis and routine examination of the sinuses (including x ray) is indicated Since chronic bronchitis is so commonly associated with emphysema pulmonary fibrosis asthma or bronchiectasis the physical findings will vary In the case of asthma which is characterized by a noisy chest it may be necessary to silence the chest first with an injection of epinephrine or inhalation of a suitable bronchodilator before the inspiratory rales of bronchitis may be heard

A simple but useful procedure in the diagnosis of chronic bronchitis is the examination of the sputum if there is expectoration It is wise to collect a twenty four hour specimen which is examined for odor volume viscosity and the presence of gross pus If ob

tained under relatively sterile conditions this may also be sub jected to bacteriologic studies including identification of organisms and inhibition testing with antibiotics

TABLE 18 COMPARISON OF CLINICAL CHARACTERISTICS OF ATOPIC AND INFECTIOUS ASTHMA

Differential Point	Atopy	Infection
History		
Family history	Usually positive	±
Season	Predictable	Cold and changeable
Cough	Late no residual	Prominent early residual
Sputum	Mucoid early or late	Late purulent
Nasal discharge	Mucoid early or late	Late purulent
Onset of attacks	Abrupt	Gradual
Precipitating factors	Foods and inhalants	Respiratory infection
Other allergy	Frequent	Infrequent
Sneezing	Frequent	Infrequent
Itching eyes	Frequent	Infrequent
Lacrimation	Frequent	Infrequent
Fever	Absent	Common
Chemotherapy	No effect	Shortens or aborts attack
Response to epinephrine and aminophylline	Good	Fair or poor
Physical examination		
Nasal mucosa	Pale translucent swelling	Red opaque swollen
Nasal secretions	Mucoid	Purulent
Uvula	Pale translucent	Red wrinkled
Tonsils	Pale	Red
Lateral pharynx	Pale	Red streaks
Chest	Asthma	Asthma
Sinuses	Transilluminate	Often opaque
Laboratory Data		
Sinus x rays	Clear or thick mucous membrane symmetrical	Opaque to hazy often unilateral
Leukocyte count	Normal	Elevated or normal
Eosinophilia	Infrequent	Common
Weltmann reaction	Shift to right or normal	Shift to left
Reaction to skin tests	Foods and inhalants prominent	Foods and inhalants not prominent

SOURCE Swineford O Asthma Classification of Causes J Allergy 25 151 (1954)

The differential diagnosis between infectious and allergic reactions in the bronchi may at times be difficult In Table 18 are listed differences which may be helpful in reaching the proper diagnosis

It should be borne in mind that frequently both factors (allergy and infection) may coexist

In a recent discussion of bronchitis and emphysema by Mayer and Rappaport[9] a point of view different from that commonly accepted is presented namely that most cases of chronic bronchitis do not develop emphysema Emphasis is placed on the fact that emphysema involves alveolar damage which is not normally encountered in bronchitis and that bronchitis per se does not therefore produce emphysema Furthermore simple bronchitis is a very common condition and yet emphysema is not so common as revealed by clinical and postmortem examination According to these observers the two conditions are frequently confused with each other because of common clinical features such as cough expectoration and wheezing resulting from bronchiolitis

ASTHMATIC BRONCHITIS ✓

Asthmatic bronchitis is a dubious clinical entity occasionally mentioned in medical literature This term seems to be used evasively by the pediatrician or general practitioner when he is not certain whether he is dealing with bronchitis in which there may be some associated wheezing or whether he is confronted with a mild type of asthma due to infection

In asthmatic bronchitis the severe paroxysmal dyspnea usually associated with asthma is lacking and therefore there is hesitation particularly on the first examination to make a diagnosis of asthma Furthermore the term *asthma* is frightening to parents but *bronchitis* is not and therefore *asthmatic bronchitis* becomes a hedging device When patients with so-called asthmatic bronchitis particularly children are followed through a number of episodes it becomes apparent that the true condition is that of asthma since ultimately dyspnea does become an important complaint Perhaps it is best to think of asthmatic bronchitis as incipient asthma associated with bronchitis The physical findings in these cases are those of bronchitis along with moderate wheezing but without dyspnea It is advisable to eliminate this term altogether and to think only in terms of bronchitis when there is no dyspnea requiring medication for relief One cannot rely on wheezing alone to make a diagnosis of asthma

BRONCHIAL ASTHMA

Since much has already been written about asthma in all its phases we concern ourselves here with asthma only as it relates to bron

chitis emphysema and bronchiectasis This eliminates from immediate attention pure allergic asthma resulting only from specific sensitization to foods drugs or inhalants This is a simple type of asthma occurring only on contact with specific allergens and uncomplicated by other respiratory disorders Many of these cases if untreated may ultimately develop severe asthma even when not in contact with the specific allergen Here secondary infection (sinusitis and/or bronchitis) has supervened and complicated the picture Asthma in this instance is of the mixed type in which the coexistence of both allergy and infection must be evaluated and treated if the patient is to be given adequate relief Asthma of the mixed type is relatively common and although it may be postulated that one is dealing here with bacterial sensitization in addition to simple allergy this may not be the case Infection seems to play a part in the production of asthma in other ways than through the mechanism of bacterial allergy[10] (see Chap 9)

Closer to the subject under consideration however is that type of asthma unaccompanied by atopy (marked family history of allergy concomitant allergies positive reactions to skin tests positive transfer tests etc) which begins relatively late in life and in which infection plays a major but as yet ill defined role (see Chap 20) This type of asthma usually labeled *intrinsic* may be accompanied by bronchitis and emphysema and less commonly by bronchiectasis Indeed many of these cases as previously mentioned may give a history of recurrent or chronic bronchitis or sinusitis before the advent of asthma Possibly some type of hidden allergy escaping the conventional methods of detection may be the explanation for this type of asthma This however remains to be demonstrated Several possibilities besides bacterial sensitization must be considered including autosensitization induction of sensitization not previously present conversion of latent or subclinical to active or clinical sensitization and the possible induction of bronchospasm by the production of pharmacodynamic substances by infectious agents

Since wheezing of varying degree may be encountered in asthma (allergic or cardiac) bronchitis or emphysema it may be difficult to differentiate among them In Table 19 are listed the differentiating features of each of these diseases

As indicated earlier generally the problem is not only to differentiate between these wheezing states but to understand their interrelationship when they coexist and to consider the role each of these may play in the total clinical picture In the interrelationship among asthma bronchitis and emphysema one factor dominates the picture *infection* It is the common thread which binds them together Proper understanding of this and attention to its control

Table 19 Differential Diagnosis of Infectious Asthma Chronic Bronchitis Bronchiectasis and Emphysema

	Infectious asthma	Chronic bronchitis	Bronchiectasis	Obstructive emphysema
Etiology	Infection	Infection (with few exceptions)	Infection	Infection
History				
Wheeze	Paroxysmal less often continuous	Usually absent	Absent	Continuous
Cough	Initiates asthma	Variable	Productive	Nocturnal
Sputum	Scant thick tenacious mucopurulent	Scant mucopurulent	Voluminous layers malodorous	Scant mucoid or mucopurulent
Dyspnea	With asthma	Variable	Late manifestation	Common on effort
Physical Examination				
Clubbing	Absent	May be present	Usual	Present or absent
Cyanosis	Absent	Absent	Absent	Common late
Percussion	Hyperresonance variable with attack	Normal	Normal or slight dullness	Hyperresonance constant
Auscultation	Sibilant and sonorous rales expiratory wheezing expiration prolonged	Inspiratory rales scattered throughout occasional slight wheeze expiration normal	Circumscribed rales no wheezing normal expiration	Diminished breath sounds mild wheeze expiration may be prolonged
Cor pulmonale	Absent	Absent	Absent	Common
Secondary polycythemia	Absent	Absent	Absent	Common
Pulmonary Function Tests				
Maximum breathing capacity	Reduced only during paroxysm	Normal	Normal	Marked reduction
Timed vital capacity	Reduced only during paroxysm	Normal	Normal	Marked reduction
Hypercapnia anoxia	Occasional	None	None	Marked

or eradication goes a long way in the amelioration of symptoms The therapeutic approach should be broadened however to include al lergy and psychodynamics It is the over all approach in diagnosis and treatment which provides the over all results

Other pulmonary diseases in addition to bronchitis and emphysema may be associated with asthma These include bronchiectasis bron chostenosis and atelectasis

BRONCHIECTASIS

The prevailing opinion among allergists is that bronchiectasis is nonallergic in origin One of us R G observed bronchograms of asthmatics in whom no evidence of bronchiectasis was found Sterns S Bullen Sr [11] noted only a 5 per cent incidence of bronchiectasis in his series of 175 cases of asthma coming to autopsy Nevertheless there are several allergists who feel that there is an allergic factor in bronchiectasis [1]

Bronchiectasis is a chronic infectious disease of the smaller bronchi characterized by structural changes in the bronchial walls that re sult in dilatation of the bronchi The histology of the bronchi ectatic walls depends upon the developmental stage of the process (inflammatory destructive or reparative) The adjacent lung is usually involved in a similar process to a greater or lesser degree The ectasia may be cylindrical saccular or cystic in form The prin cipal changes involve the peripheral bronchi with the major bronchi rarely being involved The pathologic picture is determined by the infection of the bronchial wall and the effect of the mechanical in fluences which distend the bronchus after it is weakened by the in flammatory reaction Chronic sinusitis is often a predisposing cause of the disease since purulent secretions may drip into the bronchi during sleep Infection may also occur systemically via the blood stream or the lymphatics to the peribronchial glands infecting the bronchial wall secondarily

Patients with bronchiectasis complain of chronic cough and the *expectoration of 6 ounces or more of purulent sputum daily* The breath is usually foul Hemoptysis is occasionally encountered Pain will occur if there is an associated pleuritis or pneumonitis Fatigue and malaise develop slowly and become so persistent that the patient fails to recognize them Fever and chills accompany acute infectious flare ups The physical signs are variable depending upon the un derlying pathology Pulmonary osteoarthropathy if present is in proportion to the degree of bronchiectasis Cyanosis and dyspnea occur late in the disease The nasal sinuses usually have evidence of chronic infection The diagnosis is confirmed by bronchography

It is always wise to carry out bronchoscopy at the same time to eliminate the possibility of mechanical obstruction With the advent of antibiotics the incidence of bronchiectasis has been markedly diminished

BRONCHOSTENOSIS

Prickman and Moersch[13] described this complication which they feel occurs frequently in severe asthma but usually escapes diagnosis It is a stricture like narrowing of a bronchus probably primarily inflammatory in nature It occurs as a rule in the lower lobes of the lung and is characterized by suppressed breath sounds and absent tactile fremitus Fever is a usual finding This resembles atelectasis clinically and roentgenologically but on bronchoscopy the stenosis is revealed It is surprising in view of the number of cases encountered in the Mayo Clinic[13] that so few cases have been subsequently reported

ATELECTASIS

This condition in which sections of the lung collapses following complete bronchial obstruction occurs frequently in bronchial asthma Most often the condition is not recognized because the areas involved are so small and because the condition is temporary as soon as the mucous plugs are coughed up the lung reverts to normalcy Occasionally a larger section is involved in which case such symptoms as dyspnea cough and fever may dominate the picture Characteristically one finds a shift of the mediastinum and heart to the side of the atelectasis and on auscultation the breath sounds and vocal fremitus are absent Tactile fremitus is also absent over the involved area

The following brief case history is unusual in that it illustrates chronic sinusitis chronic bronchitis infectious and allergic asthma bronchostenosis atelectasis and bronchiectasis all occurring in the same patient

A C a boy of seven was first seen by one of us (S J P) because of asthma of approximately two years duration Following examination and testing it was felt that the asthma was of the mixed type due to both sensitivity (to feathers dust and possibly ragweed) and infection The roentgenograms taken at that time revealed a normal chest and veiling of the left ethmoid and left maxillary sinus The patient was treated with penicillin aerosol with good results Early the following year however after a cold the child developed what looked like a lobar pneumonia but which on admission to the hospital and examination there turned out to be atelectasis involving the right middle lobe (Fig 24 1) Following bronchoscopy and the removal of a mucopurulent plug the atelectasis was relieved (Fig 21 2) but within forty eight hours there was a recur

rence (Fig 24 3) The patient was then treated conservatively with steam generated aerosols of aminophyllin and ammonium chloride to overcome bronchospasm and to liquefy the sputum (Fig 24-4) In addition ipecac was administered to produce emesis With this treatment the mucous plug was expelled and the atelectasis improved and finally cleared by the tenth day There was however a residue of pneumonitis which persisted for several months after which a recurrence of the atelectasis in the same area resulted in his admission to another hospital where bronchoscopy was again performed and stenosis of the bronchus noted After removal of the obstruction Lipiodol was introduced into the area and the bronchogram revealed bronchiectasis Although partial lobectomy was advised the parents refused permission and the patient was taken to Arizona for two years After his return there were no further episodes of atelectasis but the patient continued to have periodic asthma particularly during the ragweed season Injections of dust and ragweed given by his pediatrician controlled this and the patient needed no medical care during the five years the case was followed since that time

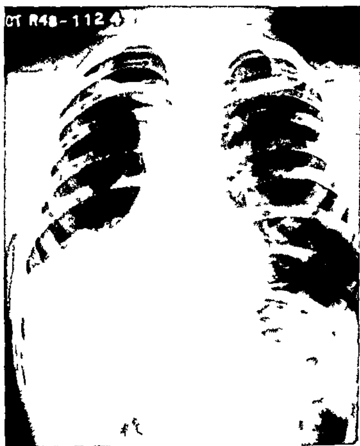
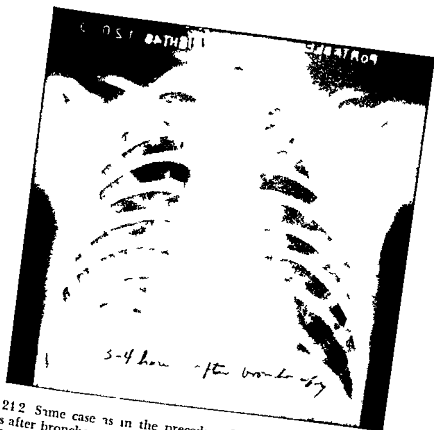


Fig 24 1 Admission x ray showing atelectasis of right middle lobe and shifting of heart and mediastinum



ig 212 Same case as in the preceding figure four days later several ours after bronchoscopy and removal of a mucous plug The atelectasis reduced and the heart and mediastinum are in normal position The ght lung is not clear there are scattered areas of pneumonitis

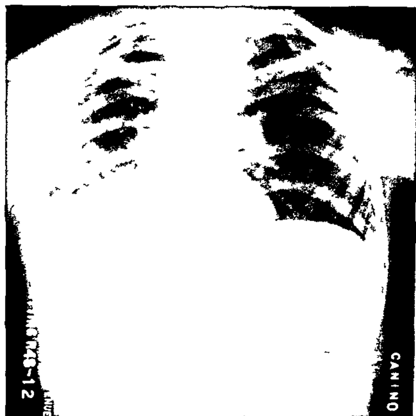


Fig 24 3 Same case showing return of atelectasis 48 hours later



Fig 24-4 Same case showing complete clearing of chest 24 days after Fig 24 3 following steam generated aerosols of penicillin aminophylline and ammonium chloride

(Films available through courtesy of Dr F Borrelli Director Dept of Roentgenology New York Medical College Flower–Fifth Ave Hospital New York City)

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Oscar Swineford Jr

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CARDIAC AND ALLERGIC ASTHMA

Cardiac asthma is thought to occur in about 8 per cent of cases of organic heart disease[1] In spite of this high incidence there have been few serious students of this intriguing syndrome Most of these students have been cardiologists who have limited their highly productive efforts to studies of the circulatory aspects of typical cases prior to 1940 There have been surprisingly few references to cardiac asthma since then The results of recent studies of the mechanisms of pulmonary edema have been applied by inference but not specifically to cardiac asthma[3] The relatively meager contributions by allergists are supplementary to and do not conflict with those of the cardiologists They are thought to broaden the practical concepts of cardiac asthma

The purpose of this chapter is to develop the thesis that the management of cardiac asthma requires in most instances the disciplines of the cardiologist and the allergist To this end current concepts of cardiac asthma are presented from the points of view of the cardiologist and the allergist together with an outline of the problems of diagnosis and management

THE CARDIOLOGIST S POINT OF VIEW

McGinn and White[4] provided the following vivid description

Cardiac asthma is a name applied to a kind of dyspnea peculiar to organic cardiac disease For this particular condition it is distinctive and is preferable to such other terms as pulmonary edema or paroxysmal dysp

nea *for it is truly asthmatic in nature and it is fundamentally of cardiac* origin Cardiac asthma is paroxysmal coming on usually in sleep but at times following exertion An attack quickly rises to a peak is accom panied by both inspiratory and expiratory difficulty and frequently by *a terrifying sense of suffocation which causes the patient to sit up or to* stand erect and even to go to the window for air The attacks last from a few minutes to a few hours averaging about an hour and leave the patient in an exhausted condition for hours or days

During an attack the physician may observe several or all of the following auscultatory signs of asthma chest held in inspiratory position respiration largely diaphragmatic inspiratory retraction of the intercostal muscles accentuation of the pulmonic second sound elevation of the blood pressure tachycardia fetal or gallop rhythm pulsus alternans ashen cyanosis cold sweat reduced and prolonged vital capacity prolonged lung to tongue circulation time increase *in the hilar shadows and fear on the patient s part that he is going* to die[1,3,5-]

The well equipped investigator may find (1) increased volume of blood in the lungs (2) normal oxygen saturation of the arterial blood or occasionally as low as 40 to 60 per cent (3) increased flow of blood into and work done by the right ventricle (4) decreased intrapleural pressure cardiac output and velocity of pulmonary blood flow (5) increased pressure in the pulmonary artery and capillaries (6) normal pulmonary artery—capillary pressure gradient (7) variable pulmonary artereolar resistance (8) increased intra thoracic pressure occasionally (9) decreased maximum breathing *capacity*[1,3,5,6]

Cardiac asthma is precipitated by acute failure of the left ventricle It is a common feature of syphilitic and hypertensive cardiovascular disease aortic valvular disease coronary insufficiency and myocardial *infarction It* occurs *but* is *infrequent* in cases of *mitral stenosis* thyrotoxicosis and other conditions which lead to failure of the left ventricle Chronic pulmonary diseases particularly chronic bron chitis emphysema bronchiectasis tuberculosis and carcinoma have been said to predispose to cardiac asthma[5,6] but on very *little* ev idence

The mechanism by which paroxysmal cardiac dyspnea is generated with or without asthma can be described as follows[5-7] When the predisposed person falls asleep the respiratory reflexes become less sensitive ventilation is adequate and there is functional balance be tween the right and left ventricles The sequence of events leading to an attack of cardiac asthma begins soon thereafter (Fig 25 1)[7] This sequence should be thought of as progressing through three

stages namely the events which precipitate those which maintain and those which relieve the attack

Factors which tend to precipitate an attack are thought to have in common the ability to change the cardiopulmonary status from that of the depression of sleep to the reflex hyperexcitability of the awakening [7] This in turn is thought to lead to increased ventilation pulmonary congestion reduced vital and maximal breathing capacities and a temporary imbalance between the right and left ventricles This sequence of events has been attributed to the supine

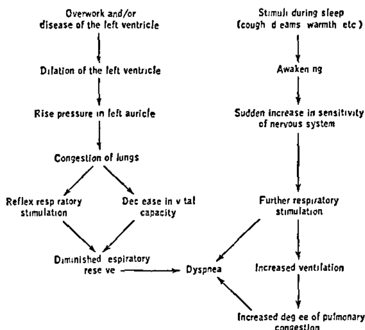


Fig 25 1 The mechanism of cardiac asthma

position resorption of edema fluid increased venous pressure decreased concentration of serum proteins decreased vital capacity during the early morning hours accumulation of bronchial mucus deep breathing cough nightmares abdominal distention constipation a full bladder hunger excessive warmth arrhythmia outside noises Cheyne Stokes respiration trepopnea nausea and vomiting decreased coronary flow during sleep the muscular effort of an attack of noncardiac asthma [7] and compression of the pulmonary veins by the enlarged left ventricle [8]

Factors which tend to maintain an attack are said to be the per

sistence of those which precipitated it plus the added metabolic demands of the cough and strenuous respiratory efforts of the attack [5-] The vicious circle of cough—increased ventilatory effort—pulmonary congestion—cough leads to pulmonary edema or to acute coronary insufficiency and death unless it is broken

Factors which tend to relieve an attack are thought to be expectoration of mucus emptying of the bladder passage of gas throwing off the bed clothes and assumption of the upright position [5-7] If these factors do not produce relief promptly the physician can relieve the attack by depressing the respiratory reflexes and cough by decreasing the return of venous blood from the periphery by decreasing peripheral vascular resistance by reducing bronchospasm and anoxemia by increasing the flow of blood in the coronary vessels and finally by improving myocardial efficiency [5 9]

Fortunately most attacks can be relieved by the administration of morphine alone or supplemented by the application of tourniquets to the four extremities (bloodless phlebotomy) The efficiency of drugs and other measures used for the relief of cardiac asthma depends on their ability to increase the coronary circulation to decrease the volume of circulating blood peripheral vascular resistance hyperventilation and bronchospasm and to restore the normal function of the left ventricle [5-7 9]

Subcutaneous administration of 16 mg of morphine is recommended usually for prompt relief of an acute attack if it is known to be due to acute failure of the left ventricle Its good effects are thought to stem from suppression of cough dulling of the hyper excitable pulmonary reflexes increased vital capacity and from decrease in hyperventilation muscle movements venous return metabolic oxygen need cardiac output and blood pressure Excessive administration of morphine may cause pulmonary edema by decreasing respiratory effort and by increasing pressure in the alveolar capillaries [9] Morphine has no diagnostic value since it relieves other forms of asthma also Since many deaths have been attributed to it morphine is rarely used in noncardiac asthma

Administration of small doses of epinephrine is effective in the treatment of cardiac and noncardiac asthma The sympathetic nerves are thought to be coronary dilators Small doses of epinephrine relax the bronchioles and arterioles increase the flow of blood in the coronary vessels and increase the functional capacity of the left ventricle [8] The subcutaneous administration of 0 2 ml of a 1 1 000 solution of epinephrine usually relieves the attack produces a prompt fall in the blood pressure and slows the pulse [1 5 6] The author has found no documented report of untoward effects from the administra

tion of small doses of epinephrine in cardiac asthma Objections to the use of epinephrine probably stem from the effects of large doses (more than 0 5 ml of a 1 1 000 solution) on angina[10] and on the blood pressure pulse myocardium and cardiac output

There are no established criteria for the choice of morphine or epinephrine in all cases of asthma A satisfactory rule of thumb is to use morphine if the attack is known to be due to acute failure of the left ventricle and to use 0 2 ml of a 1 1 000 solution of epinephrine in all other instances In practice the prompt relief of the attack and the reduction of the blood pressure tachycardia and effort of breathing have seemed to outweigh the possible but highly improbable ill effects of small doses of epinephrine

The intravenous administration of 0 25 to 0 5 Gm of aminophylline usually produces prompt relief of cardiac and noncardiac asthma Its value in treatment of noncardiac asthma is well established Since several cardiac patients have died during or immediately after intravenous administration of this drug it is necessary to reevaluate its proper place in treatment of cardiac asthma It should be administered very slowly and should be discontinued immediately if any additional distress becomes evident The relief produced by this drug is attributed to increased coronary circulation and efficiency of the left ventricle and to decreased bronchospasm and venous pressure[9]

Nitroglycerin may produce prompt relief of cardiac asthma by increasing coronary flow and decreasing peripheral resistance with resulting increase in the functional capacity of the left ventricle[1,5,6] The diagnostic significance of the effectiveness of nitroglycerin is doubtful since relief produced by the smoke from asthma powders and cigarettes in noncardiac asthma is attributed in part to its nitrite content

Digitalis is seldom used in the treatment of acute attacks because of its delayed effect In severe prolonged attacks intravenous digitalization may be lifesaving On the other hand it may intensify the heart failure through its occasional pressor effect[3] It may restore normal pressure relations in the pulmonary circuit even when the peripheral circulation is normal[5,6] In general however its chief use is to interrupt a series of attacks Unequivocal relief produced by digitalization is diagnostic of cardiac asthma since digitalis has no effect on other forms of asthma

Diuretics may be used instead of or to supplement digitalis Interruption of a series of attacks coincident with diuresis and appreciable weight loss also may be diagnostic of cardiac asthma

Administration of oxygen under positive pressure is recommended

in the treatment of persistent severe attacks because it tends to prevent pulmonary edema by opposing the increased intracapillary pressure by decreasing the amount of blood entering the right atrium and by increasing oxygen saturation of the arterial blood Prompt relief of an attack by the use of oxygen alone has diagnostic significance since oxygen does not break up attacks of noncardiac asthma

Bloodless phlebotomy is an effective procedure which rivals the effectiveness of morphine in the treatment of cardiac asthma [5] [6] This consists of the application of blood pressure cuffs to each of the four extremities The cuffs are inflated until the pressure is just above the diastolic level Since this does not relieve noncardiac asthma it is a useful diagnostic procedure It reduces the return of venous blood to the heart and allows the left ventricle to restore normal relations in the pulmonary circuit

Rapid removal of 300 to 500 ml of blood by venesection accomplishes the same thing as bloodless phlebotomy In addition it decreases the viscosity of the blood a desirable goal when there is polycythemia Obviously it should not be used if anemia is present

Antibiotics are not effective in the treatment of an acute attack of cardiac asthma or infectious asthma but they are of great value in interrupting a series of attacks as status asthmaticus precipitated by infection

Atropine application of pressure to the carotid sinus blocking the vagus nerves with procaine hydrochloride the use of general anesthesia [3] and administration of alcohol have little to commend them for routine use although they may occasionally interrupt an acute attack

Effective prophylaxis against subsequent attacks is obtained usually by digitalization and by restriction of salt Supplementary sedation at bedtime elevation of the head in bed diuretics coronary dilators reduction of weight restriction of activities and correction of anemia may be necessary for maximal results In addition venesection may be indicated if the patient is plethoric

The prognosis is poor Of the patients studied by Palmer and White [1] and by McGinn and White [4] 62 percent died within two years after the initial attack Only 8 per cent lived for more than five years The following conditions affect the prognosis adversely syphilitic heart disease coronary thrombosis angina pectoris more than one attack per day prolonged and severe attacks associated congestive heart failure gallop rhythm pulsus alterans poor heart sounds and intraventricular or atrioventricular heart block [1] The prognosis is less grave in arteriosclerotic hypertensive cardiovascular disease Au

ricular fibrillation inverted T waves and low voltage electrocardiographic complexes do not seem to affect the prognosis

THE ALLERGISTS POINT OF VIEW

The discussion so far has been equally applicable to paroxysmal cardiac dyspnea and to cardiac asthma Harrison [7] pointed out that it has not been adequately explained why wheezing occurs in some cases of paroxysmal cardiac dyspnea but not in others Allergists to whom wheezing is a major concern have paid little attention to cardiac asthma Harkavy [11] in 1924 reported four cases in which relief was not obtained until allergenic influences were removed Rackemann [1] observed rather pointedly that if cardiac asthma were commonly dependent upon simple heart failure with pulmonary stasis one would suppose that at least a large portion of patients with heart disease would show asthma but they do not Evidence was offered later [13] to support the thesis that wheezing with paroxysmal nocturnal dyspnea usually means that asthma or hay fever has been present prior to the advent of heart failure

The role of the allergist has been reemphasized recently in a review of 26 cases of cardiac asthma Several clinical observations were made which are thought to have practical value For example asthma and heart disease may run their courses independently neither seeming to influence the severity of the other Typical cardiac asthma and typical nonasthmatic paroxysmal cardiac dyspnea can occur at different times in the same patient An attack of asthma due to other causes may occur in a patient who has heart disease in which there is no evidence of heart failure Conversely heart failure may occur in an asthmatic in whom there is no intensification of preexisting asthma Mild attacks of cardiac asthma may precede a series of severe attacks A series of mild nightly attacks of cardiac asthma is not infrequent Cardiac asthma may be relieved temporarily by noncardiac management including the use of conventional symptomatic remedies for asthma Patients with severe heart disease may often avoid attacks by avoiding known allergenic influences Prompt recognition of the allergic or infectious component may provide early protection of the heart from the strain of repeated attacks

The role of infection in cardiac asthma may be quite complex Respiratory infection in a patient with heart disease may precipitate heart failure either directly or indirectly as the result of the work load of infectious asthma Other infections may precipitate heart failure directly During an attack the relative importance of in

fection and of failure of the left ventricle may be impossible to evaluate Frequently asthma will not be relieved adequately until allergy infection and heart failure have been controlled and occasionally heart failure will not be controlled until allergic and infectious loads are removed

Only 6 of the 26 patients with cardiac asthma studied with the disciplines of the allergist and the cardiologist were relieved adequately by cardiac therapy alone The other patients required cardiac plus allergy and infection therapy for maximal relief Eighteen had had asthma from other causes prior to the advent of paroxysmal left ventricular failure Twenty five all but one had other manifestations of an allergic background Fifteen had evidence of respiratory infection All had some evidence of heart failure usually from arteriosclerotic heart disease with or without hypertension

DIAGNOSIS

There are at least nine types of causes of asthma [14] allergy infection nonspecific irritants nasobronchial and bronchobronchial reflexes chronic pulmonary disease thermal and humidity changes psychogenic conditions bronchial obstruction and cardiac disease Each of these types puts its diagnostic stamp on the dyspneic wheezer

In most cases of chronic asthma multiple types of causes can be recognized readily Cardiac asthma is no exception In other words *the diagnosis of cardiac asthma should be approached with the idea* that other causes of asthma will be found in addition to paroxysmal left ventricular failure

Typical cardiac asthma should offer no diagnostic challenge Unfortunately cardiac asthma may be quite atypical [2, 5, 6] It is in this type of asthma that the disciplines of the allergist the chest physician and the cardiologist are needed

During an attack the presence of cardiac asthma should be suspected if the patient is more than forty years old is sweating profusely seeks fresh air has an abnormal left ventricular or auricular load or has a sudden fear of death The diagnosis can be confirmed if (1) the attack is relieved promptly by bloodless phlebotomy venesection or administration of oxygen under positive pressure (2) acute pulmonary edema develops (3) the lung to tongue circulation time is markedly prolonged or (4) the presence of unequivocal transient pulmonary congestion can be demonstrated It is often necessary to observe a series of attacks to interpret these observations accurately

The examination after an attack often provides useful information The presence of cardiac asthma is strongly suggested by a marked fall in blood pressure and pulse rate disappearance of moist basal rales roentgenologic signs of pulmonary congestion diuresis and marked slowing of the prolonged circulation time Between attacks the diagnosis cannot be made with certainty Cardiac asthma at this stage is most often confused with paroxysmal cardiac dyspnea without asthma

In actual practice the suspicion of the cardiac factor in asthma is seldom confirmed until a series of nightly attacks is terminated or markedly ameliorated by digitalization or diuresis A majority of patients with cardiac asthma will continue to have asthma of some degree until allergy infection or other causes of asthma have been recognized and treated

The role of heart disease may not be obvious It may not be recognized until a diagnostic trial of treatment of heart failure provides striking relief Paroxysmal cardiac dyspnea may be the first sign of coronary insufficiency [1] or the stigmata of heart disease may be so slight as to seem to preclude acute failure of the left ventricle

Since cardiac asthma is due to failure of the left ventricle signs of failure of the right ventricle such as peripheral edema large tender liver and distended veins may be lacking When the right ventricle fails cardiac asthma may be relieved temporarily [1] By the same token acute failure of the left ventricle may recur after the right ventricle fails This superimposes the syndrome of cardiac asthma on that of conventional congestive failure

The differential diagnosis presents several problems During an attack simple orthopnea evening dyspnea waking dyspnea (Cheyne Stokes) paroxysmal cardiac dyspnea and pulmonary edema are distinguished by the absence of asthma Between attacks the differential diagnosis may be impossible

The differential criteria usually mentioned do not distinguish the cardiac form from asthma due to other causes For example asthma from any cause may begin after the age of forty may be predominantly nocturnal may cause both inspiratory and expiratory dyspnea may be accompanied by sweating and cough and may be relieved by morphine

The proper diagnostic approach is to obtain all available information indicative of heart disease heart failure respiratory allergy infection [10, 17] and other causes of asthma [14] Many of the diagnostic criteria of allergy infection and acute failure of the left ventricle (Table 20) will be found in most cases of cardiac asthma if looked for

It should not be difficult to distinguish emphysema associated with wheezing from paroxysmal cardiac dyspnea associated with wheezing especially in the periods between attacks In a typical case of emphysema the onset is gradual the thoracic cage is deformed the diaphragm is flattened tachycardia is minimal the patient is not conscious of his heart breath sounds are soft basal rales are not present wheezing and dyspnea are precipitated by slight exertion the vital capacity test reveals prolonged expiration and relief is obtained by lying down Laboratory procedures reveal reduced maximal breathing capacity increased ratio of residual volume to total capacity poor mixing of pulmonary gases and lessened negative intrathoracic pressure Emphysema associated with wheezing usually is complicated by allergy or infection or by both (see Chap 24)

TABLE 20 DIFFERENTIAL DIAGNOSIS OF ALLERGIC INFECTIOUS AND CARDIAC ASTHMA

Differential criterion *	Allergic asthma	Infectious asthma	Cardiac asthma
Clinical History			
Season	Pollen or perennial	Cold	Any
Cough			
Time in attack	Late	Early	Variable
Severity	*Mild*	*Severe*	*Variable*
Residual	None	Usual	None
Discharges			
Nasal	Mucoid	Purulent	None
Bronchial	Mucoid	Purulent	None or frothy
Hay fever	Common	Not present	Not present
Fever	None	Common	None
Antibiotics	No effect	Effective	No effect
Heart disease	Not present	Not present	Present
Fear of death	Rare	Rare	Common
Air hunger	Rare	Rare	Common
Status asthmaticus	Occasional	Common	Rare
Physical Examination			
Color	Normal (cyanotic when severe)	Normal (cyanotic when severe)	Ashen
Nasal mucosa	Pale	Red	Normal
Nasal secretions	Mucoid	Purulent	None
Uvula	*Pale*	*Red*	*Normal*
Lateral wall of pharynx	Pale	Red	Normal
Sinuses	Normal	Hazy or opaque	Normal
Chest	Asthma	Asthma	Asthma
Rales	Mucous	Crepitant	Moist basal
Heart size	Normal	Normal	Enlarged †

TABLE 20 DIFFERENTIAL DIAGNOSIS OF ALLERGIC, INFECTIOUS AND CARDIAC ASTHMA (*Continued*)

Differential criterion	Allergic asthma	Infectious asthma	Cardiac asthma
Blood pressure	Normal	Normal	High †
Arrhythmia	None	None	Frequent
Pulse rate	Increased, decreased or normal	Increased, decreased or normal	Increased
Pulmonic second sound	Normal	Normal	Accentuated
Cold sweat	Rare	Rare	Common
Circulation time	Normal	Normal	Prolonged
Response to Therapy			
Antimicrobic	None	Good	None
Epinephrine	Excellent	Fair	Good
Aminophylline	Excellent	Fair	Good
Morphine	Good	Good	Excellent
Digitalis	None	None	Excellent
Tourniquets	None	None	Excellent
Venesection	None	None	Excellent
Positive pressure O	None	None	Good
Nitrites	Fair	Fair	Good
Laboratory Tests			
Sinus x rays	Not helpful	Helpful	Normal
Leukocyte count	Normal	Frequently increased	Normal
Eosinophil count	Normal	More than 5%	Normal
Skin tests			
Food and inhalants	Positive	Not helpful	Not helpful
Bacterial antigens	Not helpful	Not helpful	Not helpful

There are occasional exceptions. Signs of allergy, infection, and cardiac asthma *often occur simultaneously*.

† May be normal in arteriosclerotic heart disease.

TREATMENT

The treatment of cardiac asthma is rather routine after the role of paroxysmal failure of the left ventricle has been recognized and the other noncardiac causes of asthma have been evaluated. Attacks of asthma and the underlying heart failure are controlled by the measures described. Treatment of allergy consists of the avoidance of offending foods and inhalants and the injection of extracts of inhalant allergens which cannot be avoided. Infection should be treated promptly and persistently, until cured, by specific drugs and other appropriate therapy. The paranasal sinuses should receive particular attention.

COMMENT

Important problems remain in spite of good and at times dramatic results of treatment of cardiac asthma For example no real effort has been made to find a common factor in the several types of *heart disease in which paroxysmal cardiac dyspnea occurs* The absense of this factor might explain why paroxysmal cardiac dyspnea occurs in relatively few patients with hypertension coronary thrombosis or other left ventricular loads

What are the differences between paroxysmal cardiac dyspnea and pulmonary edema? How does infection lead to cardiac asthma? Why does a patient have asthma in one attack and not in the next? Do the supposed factors really precipitate maintain and relieve the attacks? What are the differences in the sputum ciliary action and mucosal morphology and function between paroxysmal cardiac dyspnea and cardiac asthma?

Comprehensive management of allergy infection and heart disease usually provides better clinical results than cardiac therapy alone. Is there a comparable improvement in prognosis? Is the prognosis better in paroxysmal cardiac dyspnea than in cardiac asthma?

Cardiac asthma is less common since penicillin has effectively lowered the incidence of cardiovascular syphilis Will the incidence and prognosis of cardiac asthma be reduced further by antiarteriosclerosis and antihypertension measures by the widespread substitution of foam rubber and other synthetics for feathers and crude cotton in beds and upholstery and by the earlier effective control of allergy and infection?

Cardiac asthma is a difficult problem to study Attacks usually occur at night at home at unpredictable times and tend to subside spontaneously within an hour or so The effects of measures used for relief are therefore easily misinterpreted

The newer methods for studying the circulation and pulmonary function should be applied to paroxysmal cardiac dyspnea with *and without wheezing Proper evaluation of these new physiologic* and pharmacologic studies and the roles of allergy and infection will require crews of well equipped trained observers readily available for immediate action whenever the opportunity arises This seems feasible only in the emergency rooms and wards of large metropolitan hospitals

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26 | *Laurence Farmer*

SYMPTOMATIC TREATMENT OF ASTHMA

Considerable progress has been made in recent decades in the treatment of bronchial asthma In speaking of this progress the main emphasis is usually placed on the recognition of the etiologic importance of hypersensitiveness in this condition and on the ensuing advances in the causal therapy of asthma Little mention is made of the progress achieved during this period in its symptomatic treatment How much has been added here also becomes evident from a perusal of the 1901 edition of Osler s *Practice of Medicine*

Inhalation of a few whiffs of chloroform and spirits of chloroform in hot whisky injections of morphine cocaine pilocarpine smoking of tobacco and asthma cigarets belladonna and lobelia by mouth inhalation of oxygen and finally potassium iodide (of which Osler says there is no remedy as useful in preventing the recurrence of attacks)—these comprised the physician s armamentarium in the treatment of bronchial asthma

In 1903 a turning point was reached with the introduction of epinephrine which has remained superseded by none the supreme drug in the symptomatic treatment of the asthmatic attack Its action is rapid and a subcutaneous injection of 0 3 to 0 4 ml of a 1 1 000 aqueous solution can usually be counted on to terminate even the most severe paroxysm The comparatively short duration of its effect often necessitates a second or third injection or the additional intramuscular administration of 0 5 to 1 ml (1 to 2 mg) of a 1 500 suspension of epinephrine in oil The suspension is longer acting

but slow in onset and should not be used in an emergency For milder attacks oral inhalation of a concentrated (1 100) aqueous solution will often suffice

Besides epinephrine a number of other sympathomimetic drugs are of definite value in the treatment of bronchial asthma One of the newest members of this group isopropyl norepinephrine marketed under various trade names such as Isuprel Norisodrine and Aludrine has proved to be very effective when used sublingually (10 to 15 mg) or by inhalation It is also often effective in patients who have become epinephrine fast

Bronkephrine (ethylnorepinephrine) 0 5 to 1 ml subcutaneously although not so potent as epinephrine is often efficacious It has less pronounced pressor action and makes the patient much less jittery

Ephedrine (hydrochloride or sulfate) which has found wide use especially in the treatment of protracted asthma is one of the main components of many proprietary compounds It can be given parenterally but it is commonly used orally in doses of 25 to 50 mg (3/8 to 3/4 grain) three or four times a day Propadrine hydrochloride by mouth in the same dosage is preferred by many patients in whom ephedrine produces palpitations and nervousness

Next to the subcutaneous administration of epinephrine the intravenous injection of aminophylline (theophylline ethylenediamine) 0 25 to 0 5 Gm in 10 or 20 ml of water affords the most rapid relief of asthmatic dyspnea To avoid possible untoward reactions aminophylline must be injected very slowly Intramuscular injection of 0 5 Gm in 2 ml of solution relieves paroxysms more slowly and less dramatically but still very effectively Glucophylline (theophylline methylglucamine) is less painful than aminophylline on muscular injection and equally efficacious (0 732 mg in 2 ml)

On parenteral administration the concentration of aminophylline in the bloodstream rises rapidly but is not maintained very long Where it is desirable to have higher blood levels for a prolonged period of time aminophylline should be given orally (0 2 Gm three or four times a day) or by rectal suppository (0 5 Gm two or three times a day) Numerous patients complain of rectal irritation following the use of these suppositories Rectal instillation of 0 5 Gm of aminophylline dissolved in 15 to 30 ml of tap water usually overcomes this difficulty

The inhalation of oxygen long used in the treatment of asthma and still widely prescribed preferably by mask or nasal catheter is very efficacious in relieving dyspnea Although this form of therapy is generally thought to be innocuous it should be pointed out that

infrequently mental confusion stupor coma and death may occur during the inhalation of oxygen in bronchial asthma associated with chronic emphysema The explanation offered is that the high oxygen concentration of the inspired air rapidly and fully saturates the arterial blood and abolishes the anoxic stimulus to breathe in patients who are already laboring under the effects of an elevated carbon dioxide blood level The ensuing decrease of ventilation and failure to eliminate carbon dioxide in turn results in further increase in blood carbon dioxide to dangerous and even fatal levels To minimize and obviate such occurrences the administration of oxygen should be carefully supervised and periodically interrupted

Atropine and morphine formerly widely used in the treatment of asthma have come into disrepute Morphine especially is regarded as absolutely contraindicated by most allergists In their place Demerol an atropine like drug with strong analgesic action has found great favor and its parenteral administration in severe asthma has become an almost routine procedure in some quarters The pronounced mental confusion we have seen in several instances following the injection of Demerol however has made us question the wisdom of using this drug

Reassurance and sedation of the often apprehensive asthmatic patient are of prime therapeutic importance In prescribing sedatives especially in chronic cases complicated by emphysema recourse should be had to drugs which do not depress the respiratory center Chloral hydrate 0 5 to 1 Gm as a soporific or in doses of 0 25 Gm three times a day as a daytime sedative should be used more widely than is customary at present By the same token greater restraint should be exercised in the use of the barbiturates

The antihistamines in contrast to their efficacy in other allergic diseases are of little value in the treatment of bronchial asthma

The often profuse production of copious tenacious sputum tends to augment the asthmatic s dyspnea and frequently contributes greatly to his discomfort Inspissation of the sputum and blocking of the bronchioles can even endanger his life Evacuation of the sputum is one of the most important measures in the symptomatic treatment of asthma Potassium iodide one of the oldest antiasthmatic drugs has proved to be one of the most efficacious and has not been replaced by any of the newer expectorants Ten to fifteen drops of a saturated solution (equivalent to 1 to 1 5 Gm) two or three times a day often works wonders Osler s view that potassium iodide sometimes acts like a specific is undoubtedly shared by most of those who have had wide experience with it

Where iodides are contraindicated as in pulmonary tuberculosis

or where they are poorly tolerated syrup of ipecac may be tried It is often very effective Terpin hydrate so widely prescribed in chronic cough lessens abundant sputum and therefore should not be used in patients with tenacious sputum In cases where the patient is unable to empty his bronchi actively suction by catheter introduced through a bronchoscope has a definite place and has been lifesaving

The greatest boon to the asthmatic since the introduction of epinephrine is the advent of the corticosteroids and of corticotropin Cortisone and its congeners and ACTH although purely symptomatic in their actions and without curative value frequently afford so great a degree of relief that they are truly a blessing for the harassed sufferer in status asthmaticus The use of these hormones in allergic diseases and their indications and limitations are discussed in Chaps 34 and 57 However it should be stressed that these drugs should not be used for the emergency treatment of bronchial asthma Here as in the past aqueous epinephrine remains the drug of choice

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Russell Clark Grove

SURGICAL TREATMENT OF SINUSITIS ASSOCIATED WITH ASTHMA

When I first became interested in the treatment of sinusitis associated with asthma over twenty five years ago it was one of the most controversial subjects in the field of allergy Few allergists and otolaryngologists conceded that infection in the sinuses caused asthma and they opposed any sinus surgery as a form of treatment for asthma

Cooke[1] has been the foremost proponent of infection as a cause of asthma and many physicians are in agreement with his theories I shall try to present evidence in this chapter to show that surgery on the sinuses is worthwhile when there are proper indications and when the sinus infection is removed as completely as possible

A thorough medical and allergic work up is essential in determining the etiologic factors in any case of asthma One must be certain that the patient has true bronchial asthma It is axiomatic that all that wheezes is not asthma It must be determined whether there is evidence of a foreign body tuberculosis or cancer in the lungs It is necessary to obtain a concise history of the beginning of the asthma and its subsequent course in order to decide whether infections environment, contacts or foods play a role in the case After complete skin testing the positive reactions must be evaluated to determine which ones may be important in causing the asthma

I have emphasized this thorough study because it is most essential to know with what type of asthma we are dealing before deciding on any surgical treatment of the sinusitis In other words is the asthma

caused by sensitivity to certain allergens by infections or by a combination of both factors? If the asthma is caused by house dust pollens feathers animal contacts or foods sinus surgery will not be helpful If however associated upper respiratory infections produce additional attacks of asthma then sinus treatment must be considered I feel that many of the poor results obtained with sinus surgery in asthma are due to the improper selection of patients

When the otolaryngologist first sees the asthmatic patient he must examine the sinuses carefully Evidence of pus or polyps in the nose should be sought with the nasopharyngoscope Roentgenograms of the sinuses should be made since polyps or cysts may not be demonstrated by transillumination If there is still doubt as to the diagnosis a radiopaque medium should be introduced into the sinuses Lavage of the maxillary sphenoid or frontal sinuses may be done However a clear return flow does not always mean that there is no infection present In the hyperplastic type of sinusitis seen in asthmatic patients the infective agents are deeper in the tissues of the hyperplastic sinus membranes and often on the surface only during an acute respiratory infection Furthermore the gob of thick white discharge washed out is usually not infected when cultured but this has nothing to do with the underlying primary infection in the sinus membranes

The maxillary sinuses are most frequently infected the ethmoids second the sphenoids third and the frontals least often Polyps are found in about 15 to 20 per cent of the patients who have not had any previous sinus surgery Cooke[1] in a study of 470 patients over ten years of age found that sinusitis was the only cause of the asthma in 45 per cent

The allergist and otolaryngologist should consult with each other regarding the etiologic factors and the proper treatment In many patients treatment of the allergic factors and the use of autogenous or stock vaccines may be helpful However when the infection is the active cause of the asthma and there are sufficient pathologic changes present operation should be performed Antibiotic and steroid hormone treatment is only palliative

When surgery is performed it should include removal of the infected membranes and polyps from all the sinuses involved Often a Caldwell Luc operation is performed and polyps are left in the ethmoids or a single Caldwell Luc or ethmoid operation is done when a bilateral operation is necessary Not too long an interval of time should elapse between the two-stage operation I have found that the quicker all the infection is removed the better are the results It is necessary to emphasize that complete removal of the in

fected membranes is essential because our results show that simply removing a nasal polyp without doing an ethmoidectomy or making a window into the antrum (antrostomy) does not suffice to eliminate the infection and produce benefit

In evaluating the results of the surgical treatment of sinusitis in asthmatic patients it is necessary to consider the effects on the sinuses themselves and also on the asthma When the surgery is done completely I feel that not more than 20 to 25 per cent of the results are unsatisfactory in the nose Other otolaryngologists[2] quote higher percentages Even with a recurrence of nasal polyps patients may still remain free of asthma Postoperative treatment with antibiotics and the steroid hormones particularly Meticorten is most helpful in promoting good healing and avoiding a recurrence of the polyps

Since 1935 we have made six comprehensive studies of the results of sinus surgery on patients with asthma These patients were divided first into two groups depending on the cause of the asthma namely infection or infection plus sensitizations They were further divided into those who had had complete surgery and those with incomplete surgery The group in which asthma was caused by infection plus sensitizations was more improved than the group with pure infection The group which had had complete surgery showed over twice as much improvement as that with incomplete surgery The best results were obtained in the patients with associated sensitizations probably because in these cases the infection was merely a secondary factor The poor results obtained in the incomplete surgery patients were due to the difficulty in eliminating all of the infection and to the probable extension of secondary infection to the cervical and bronchial lymphatic glands and the bronchial mucosa It is important that all secondary infections in the teeth tonsils and adenoids be removed Autogenous vaccines made from sinus discharge or infected membranes removed at operation have been used postoperatively When indicated house dust injections have been given and these injections often aid in obtaining a better result in the healing of the sinuses

My most recent survey of sinusitis in patients with asthma who were treated by surgery comprises 300 patients who were followed for periods up to twenty three years (Table 21) These patients are divided into postoperative periods of one year except for the first six months This period is excluded because temporary relief may be due to the general anesthetic agent or temporary deterioration may be due to the surgical handling of the infected sinus membranes The results shown in the table compare favorably with most

of our past six surveys The group with associated sensitizations and that which had been operated on completely comprised the greater number of improved patients

TABLE 21 RESULTS OF SURGERY OF THE SINUSES IN 300 CASES OF ASTHMA

Postoperative period (years)	Number of cases	Improvement		
		1 plus	2 plus	3 plus
½ to 1	24	9	10	5
1 to 2	36	9	19	8
2 to 3	30	7	14	9
3 to 4	40	13	18	9
4 to 5	24	3	13	8
5 to 6	16	7	4	5
6 to 7	9	4	3	2
7 to 8	53	19	18	16
8 to 9	15	8	4	3
9 to 10	9	6	3	0
10 to 11	5	1	0	4
11 to 12	10	1	7	2
12 to 13	8	3	3	2
13 to 14	6	1	3	2
14 to 15	4	1	2	1
15 to 16	4	0	2	2
16 to 17	2	0	1	1
17 to 18	1	0	1	0
18 to 19	1	0	0	1
19 to 20	1	0	0	1
20 to 22	1	0	0	1
22 to 23	1	0	0	1
Total	300	92	125	83
		30.66%	41.66%	27.66%
			69.3%	

1 plus slight or no improvement 2 plus definite improvement 3 plus no asthma or rare attack

There are many studies on the effect of sinus surgery reported in the literature Some[3] are favorable while others are discouraging To some extent the disagreement may be due to different criteria used in deciding what represented infection in the sinuses in allergic patients Whether sufficient pathologic changes were present to justify operation how completely the infection was re

moved and whether all associated sensitizations were treated will also affect the surgical results If these criteria are met the treatment of sinusitis in patients with asthma should be surgical when indicated and the proper surgery will produce favorable results

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CLIMATE AND ASTHMA

The observations on the relation of climatic factors and asthma recorded through the centuries and in our times are paradoxic Perhaps this can be understood from the point of view of the complexity of this relationship Climate is a composite of multiple meteorologic factors such as temperature humidity (precipitation cloudiness sunshine) barometric pressure wind and evaporation In addition the air borne elements such as dusts pollen molds smuts danders industrial contaminants and even cosmetic particles become an integral part of climate and provide potent allergens capable of invoking asthma Furthermore the cause of asthma varies with the individual Although his symptoms may be indistinguishable from those of any other asthmatic their underlying cause or causes may be entirely different In general etiologically asthma may be atopic that is due to reagin provoking elements bacterial due to various bacteria physical due to physical agents such as heat light cold or to any possible combination of these categories With so many possibilities of interaction and the specificity of etiology in each case of asthma it is not surprising that few generalizations can be made on climate and asthma

BAROMETRIC PRESSURE

As far back as 1698 Floyer [1] wrote that a drop in barometric pressure and excessive humidity are injurious to the asthmatic To date relatively few controlled experiments have been made in this area

The most frequently mentioned observations in the literature are those of Rappaport Nelson and Welker[9] They confined seven patients with pollen asthma in a pollen free room and observed them through several abrupt changes in weather On one occasion there was a sudden pressure fall and a rise in humidity That afternoon it rained heavily That evening all seven patients had asthma Some days later there was rain again but this time it was not preceded by a sharp barometric drop or a marked temperature variation and the patients did not have asthma From this is was concluded that asthma could be induced (despite absence of pollen) by weather changes particularly a falling barometric pressure

In a survey of the Chicago area made by Petersen[3] he found that there was a marked increase in asthmatic deaths during times of change in cyclonic front (polar infall) when the barometric pressure dropped

To this day the consensus among allergists is that prestorm weather adversely influences many asthmatics This is not a general rule however and there are many asthmatics who remain unaffected by such weather

How a falling barometric pressure adversely influences asthma is still a matter for speculation Some believe that the already labile vascular bed of the bronchiolar mucosa dilates with a sudden drop in external pressure This leads to exudation narrowing of the bronchiolar lumen with its secondary effects—mechanical nervous secretory (dyspnea mucus secretion and accumulation muscular spasm)—and clinically asthma

WIND DIRECTION AND VELOCITY

The direction and velocity of wind have also been noted to induce attacks of asthma Those asthmatics who suffer exacerbations when walking into a strong wind especially if it is cold must be suspected of allergy to cold Duke[4] reports a number of such cases and indeed records several fatalities due to cold wind (see Chap 44) Again the literature is replete with reports of winds from particular directions being at the base of asthmatic attacks Van Helmont[1] and Bray[3] accuse the east wind in England This wind is continental in origin and properly may be suspected of bringing with it many airborne allergens either in greater concentrations than normally present in England or entirely foreign to it There have been periods in New York City when winds coming across the New Jersey marshes have been responsible for severe exacerbations of hay fever and asthma thought to be due to the pollen of ragweed (some say wild rice)

which flourishes in these areas At other times there have been severe symptoms from winds coming from the northwest down the Hudson River due to large quantities of corn pollen blown from especially good crops of corn in these areas Winds also have been known to bring with them concentrations of molds and to blow insects far out of their usual habitats and thus induce asthma Not so many years ago when there were serious forest fires in Canada north winds brought with them irritants that caused exacerbations of asthma in New York in near epidemic degree

Even the gentle winds that course within short distances may carry industrial contaminants throughout a city and its environs and produce difficulty for the asthmatic The smut of infested crops may also be carried by the wind and cause trouble

Winds are known to carry airborne particles for hundreds of miles so that a wind from a particular direction causing difficulty must be suspected of bringing with it irritants or allergens indigenous to the areas over which it passes

HUMIDITY

Generally speaking marked increases in humidity are bad for the asthmatic patient The water content of the air depends primarily on the temperature and the available evaporating surfaces such as rivers seas damp earth and vegetation and also on the gaseous pressure and wind velocity At times of great humidity there is interference with surface evaporation followed by an increase in the respiratory rate and lowering of the blood carbon dioxide This tends to alkalosis and it is at this point according to Petersen that clinical episodes in predisposed individuals will appear Whatever the actual dynamics there is enough clinical evidence to indicate that excessive moisture in the atmosphere is difficult for a great many asthmatics Van Leeuwen[6] Tiefensee[1] Black[7] and Salter[8] among many others have made such observations Vaughan reports a statement of Rowe s[9] that patients in San Francisco who suffered from asthma could travel a few miles inland and obtain relief

Fogs notoriously produce difficulty On the other hand the pollen asthmatic will often find his greatest relief during very humid weather and rains The increased moisture in the air usually means quiescent winds both of these characteristics militating against the movement of pollen in the air Rains wash pollen out of the air Rain is also beneficial to many asthmatics living in cities in which the air is contaminated with irritant industrial particles

Humidity may be troublesome in still another way to the asth

matic particularly the asthmatic whose difficulty is due entirely or in part to bacterial allergy Humidity may lead to infection either in a previous focus such as the sinuses or the bronchial tree or in the upper respiratory tract Such infection provokes exacerbation of asthma

Humidity however cannot be thought of simply as a deleterious characteristic of climate for the asthmatic Common is the asthmatic whose trouble arises from lack of humidity that is from an excessively dry atmosphere The first days of autumn within the house when the radiators are turned on after a summer s disuse are often times of trouble for the asthmatic Here not only the dry heat but also the dust dispersed by the radiation are causes of difficulty

Despite what is commonly said about humidity a dry climate with a sandy soil is no panacea for the asthmatic either In the hot desert areas of this country many asthmatics find themselves in great difficulty not only because of sensitivity to local flora but also because of the alkalinity of the desert dusts which may act as bronchial irritants and cause attacks of asthma

TEMPERATURE

When temperature seems to be a troublesome climatic factor this is often a result of physical allergy There are asthmatics who will react to heat or cold just as they react to material allergens such as dust or pollen Often the person allergic to cold is allergic more to a drop in temperature than to a temperature of any particular degree For this reason such individuals may experience symptoms in any season of the year during those times when temperature drops suddenly Those allergic to heat are also usually allergic to sudden rises in temperature and therefore they too may experience symptoms on this basis during any season of the year

SUNLIGHT

Allergy to sunlight is not uncommon Asthmatics may be truly allergic to sunlight or they may be allergic to other environmental elements that make their appearance with the first constant sunlit periods Early in the speculation on allergic manifestations hay fever and pollen asthma were thought to be caused by the rays of the sun This was simply because the periods of pollination began when the sun of late spring came and remained in a relatively unclouded sky Nevertheless the allergist sees patients in whom sun sensitivity

itself is the cause of trouble. (For further discussion of this type of physical allergy see Chap. 44.)

ALTITUDE

In Europe particularly the salubrious effect of altitude (above 4,500 ft.) on asthma has been reported repeatedly. This does not seem to be the general experience in the United States. Once more, when this factor (not strictly a climatic one in the specific sense) is mentioned in relation to asthma, it must be examined from the point of view of hidden effects. High altitude is usually recommended to people living at low levels. A change from their usual environment may mean a radical change in many other elements besides height above sea level. Thus going into a hilly or mountainous area means, without question, change in flora, probably change in humidity, and even change in house environment. Is it the height above sea level, then, that is beneficial at times, or is it a change in all other environmental factors? Vaughan states that despite the general conception of Arizona as an excellent climate for asthma, pollinosis is a real problem there. The alkaline desert dusts, too, are disadvantageous. If benefit is derived, it is probably not from altitude itself but rather from the dryness of the climate, which militates against infections such as sinusitis and bronchitis.

In an attempt to explain the European contention about the benefit of altitude, a number of studies have been made. These have pointed to reduced dust content of the atmosphere at higher altitudes and biochemical changes in the blood similar to those noted by Petersen.[3] Schneider[1] reported that the alkalinity of the blood was reduced at higher altitudes. From both his and Petersen's point of view, this is beneficial to the asthmatic. However, clinical experience with acidification of the blood as a therapeutic measure and also as a prophylactic has not borne out this thesis.

COMMENT

To this day the physiologic dynamics in response to climatic factors remain obscure. Curry[10] claims to have discovered a new substance in the air which he calls Aran. He relates the concentration of this substance to various weather phenomena and believes that this is the direct cause of symptoms in most patients. Although it is a provocative idea, no corroborative work could be found.

From the foregoing it is obvious that little can be said specifically

about the climatotherapy of asthma Because of the uncertain results of treatment and the multiplicity of factors involved in asthma climatotherapy usually is a last resort Certainly the patient must be given the benefit of every known mode of conventional treatment before he is uprooted and assigned to another climate If however such a pass is reached the new climate must be carefully selected on the basis of all that is known about the patient

Sir Hyde Salter[8] whose classic treatise on asthma written in the nineteenth century is still a mine of information concluded

consequently it is impossible to predict what will be the effect of any given air but that probably the most opposite to that in which the asthma seems worse will cure This is still an excellent rule of thumb We can be somewhat more specific today since we have a better idea of what constitutes this air The chosen area should also be (1) as free as possible of atmospheric allergens and irritants known to affect the patient (this will require knowledge not only of the flora of the area but also of its industrial configuration) (2) for the bacteria sensitive patient as little conducive to infection as possible especially upper respiratory infection (this may mean choice of a rural rather than an urban area) (3) for the asthmatic who is allergic to heat or cold not only the proper mean temperature but also an area with a fairly constant temperature

Finally it should be emphasized that introducing climatotherapy does not mean jettisoning conventional therapy This must be continued wherever the patient is sent until his symptoms have been relieved and do not recur for a reasonably long period

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A PROGRAM FOR THE REHABILITATION OF ASTHMATIC PATIENTS

The need for rehabilitation of the physically disabled has pyramided to alarming magnitude in the last decade. The increase in an older age population, better preventive medicine, and improved medical care are factors which elevate this problem to a high degree of importance. Rehabilitation, named by Rusk the third phase of medical care, has become an integral part of the medical responsibility of all physicians. It is estimated that there are about 28 million individuals in this country who are disabled with some sort of known physical or mental impairment. Many of them are unemployable for reasons of age or irreversible total disability. There remain at least two million disabled persons in this country, including asthmatics, who could and should be rehabilitated and placed in employment or in more productive jobs.

In addition, chronic diseases and resultant disabilities have a tendency to increase with each year, with an additional 250 000 persons becoming disabled annually. Chronic diseases not only cause physical suffering, they promote emotional disturbances, disrupt homes, break up families, and cause tragedies. These disabling diseases are very costly. It is estimated that the annual loss from disability of workers alone is in the neighborhood of 5 5 billion dollars.[1] A survey by the Task Force on the Handicapped, Office of Defense Mobiliza

tion under the chairmanship of Dr T G Klumpp[2] shows clearly the economic aspect of disabling disease

It is known that the chronically disabled asthmatic like other disabled persons may get relief from the Department of Welfare or other institutions of public assistance at the rate of $80 monthly while off his job If the asthma progresses and the patient is unable to take care of himself he will be placed in a nursing home at the expense of about $150 a month In case of hospitalization the city will spend about $26 50 a day or $800 monthly, for the patient It is clear that a small percentage of this money spent for rehabilitation could restore the health of the patient and save thousands of dollars of public money

The process of rehabilitation should start as soon as the diagnosis is made and continue until the patient returns to work Rehabilitation is a process by which a patient is returned to his greatest physical mental social vocational and economic usefulness and if employable is provided an opportunity for gainful employment Rehabilitation is not only a socially desirable and economically practical program of public policy but a right of the disabled man woman or child The need for rehabilitation exists in all cases whether mild moderate or severe Patients in all economic groups can benefit from such a program The rate and goal of rehabilitation must be individualized and must be commensurate with the physical and emotional improvement of the patient Consciously or unconsciously rehabilitation is practiced in varying degrees by all physicians although not as a separate entity

Bronchial asthma plays a prominent role in causing disability According to Spain and Cooke[3] there are about five and-one half million people in the United States suffering from bronchial asthma The incidence of bronchial asthma in industry according to Spain and Fontana[4] is the same as in the general population about 5 per cent The absenteeism from work due to asthma asthmatic bronchitis and hay fever as estimated by the same authors is 50 per cent higher than that due to any other disease As to age 30 per cent of asthmatics studied by Fuchs[5] in the allergy clinic of the University Hospital were over fifty

Patients suffering from noninfective asthma have a good chance of recovery by the elimination of the offending agent or agents and proper immunization In cases where the patient does not respond to hyposensitization treatment and in those with infective asthma of long duration the pathologic changes are often advanced incapacitating the patient for months years or life Emphysema degenerative changes in bronchial cartilage thickening of the bronchiolar

wall and the walls of blood vessels and increase in connective tissue with diminished elasticity of the lungs are the result of long standing bronchial asthma and the cause of prolonged disability

Chronic asthmatics in most instances are unable to perform their daily work and cannot be employed in many industries They can not perform exhausting physical work and many of them have to avoid dust smoke and various fumes prevalent in big cities There fore they have to be rehabilitated

Recognition of the need for rehabilitation of asthmatic patients was stimulated by the statistical data of Love and Davenport on drafted men which show that during World War I men were re jected by the draft boards of the United States Army at the rate of 2 15 per 1 000 because of asthma associated with emphysema and bronchitis As far as World War II is concerned available data re veal that the rate of rejection by the draft board of men suffering from asthma was 5 4 per 1 000 [6]

When considering the rehabilitation of an asthmatic patient it is essential to make a detailed survey of his disability and his remain ing potentialities on which he can base his future Accurate diag nosis forms the basis for estimating rehabilitation

The study of rehabilitation problems in asthmatics must consider the history physical findings thorough examination including skin testing and causative agents involved Special attention should be paid to the following (1) evaluation of the functional capacity of the lungs (vital capacity etc) (2) social service studies of the patient and his environment (3) psychiatric consultation (4) vocational counseling and selective placement which consider the age race previous training educational background skill levels job oppor tunities and the patient s capacity to work and (5) physiotherapy

A complete history and thorough physical evaluation is the first step for a diagnosis A good history will reveal the cause of the dis ease and the onset scope and character of the allergic circumstances which expose the patient to an attack of asthma or precipitate other debilitating allergic phenomena A physical examination including an ear nose and throat survey will show what physiopathologic changes have taken place in the chest mucous membranes skin or other organs and whether these changes are reversible or irreversi ble All these procedures play an important role in a functional diag nosis and help to analyze the extent of permanent disability Com plete skin testing with fresh and potent extracts and x rays of the lungs and sinuses are additional aids to the diagnosis

The patient who is asthmatic must be studied as an individual His asthma must be evaluated against the background of his occupa

tional and home environment physical and psychologic therefore a detailed social history of the patient and his environment is essential A home visit by a social worker not only may help to elicit the offending factor responsible for the patient s allergic condition but contributes to an understanding of the patient s behavior at home and the influence of the environment on his emotional status The social worker should be interested in the patient s personality temperament and attitude toward his environment the meaning of the illness to him his emotional response to his disease and his family and economic problems The social worker also should investigate the patient s job history skills work attitude and transportation problems

A good social worker should not miss the importance of social opportunity as a factor in successful rehabilitation Disabled persons need treatment and training to enable them to learn to use what they have left but for successful rehabilitation they must also have not only the will to use their abilities but the opportunity to use them

Sometimes psychologic factors initiate or aggravate attacks of asthma in sensitive patients Psychologic factors are of special importance in those cases in which the symptoms and etiology are not as clear-cut as in typical attacks of bronchial asthma (see Chap 8) Psychiatric consultation is advisable in all cases in which there is a need for emotional evaluation and supportive therapy Much of the emotional difficulty is based on fear anxiety and tension therefore the patient should not be hastily advised that it will be necessary for him to change his whole way of living Physical disability complicated by the shock of work stoppage may cause personality deterioration in a worker who cannot continue to meet his responsibilities If the disability lasts for a long time he may feel threatened and insecure and may suffer a whole series of personality changes that may decrease his rehabilitation potential

Next physiotherapy is one of the modalities which plays a role in the rehabilitation of the asthmatic patient Some physiatrists use breathing exercises to empty the lungs of the asthmatic patient by improving the expiratory phase of respiration The exercises also are designed to enhance diaphragmatic movements decrease the thoracic type of breathing and relax contracted muscles These exercises may also improve kyphosis and mobilize the ribs and chest wall Exercises may be helpful in the treatment of asthma but they are not decisive Physiotherapy can only be adjunctive therapy The following exercises for asthmatic patients should be performed in front of an open window in the morning before breakfast and at night before retiring

EXERCISES FOR THE ASTHMATIC PATIENT

Abdominal Breathing (a) Lying with knees drawn up and with hand on upper abdomen feel fingers sinking in on breathing out (contracting abdominal muscles) Then relax abdominal muscles while taking a short breath taking care not to let upper part of chest move on breathing in (b) Sit with back supported With hands over lower ribs wrists well back and fingers pointing forward begin to breathe out while contracting the abdominal muscles Squeeze the ribs at the end of the breathing out to force out the last possible bit of air Then relax the abdominal muscles and expand the lower ribs while taking a short breath The shoulders must be lowered and the arms quite relaxed until the final squeeze The aim of this exercise is to expand and contract the lower ribs as well as the upper abdominal muscles so as to use to the fullest capacity the bases of the lungs

Loosening Exercise for Shoulders Sit with feet apart hands to shoulders and elbows held out from the sides level with the shoulders Carry the elbows slightly forward then upward then backward then downward Repeat quickly six to eight times Then rest dropping arms to sides to relax shoulders Note that the back should be held straight the lower part being pressed back (against a doorway edge if necessary with a pad in the lower part of the back to maintain apposition) this may be done either sitting on a stool or standing with the feet well forward

Windmill exercise for children Stand with feet apart Both arms are circled so that they cross each other coming upward in front of face The circles then intersect each other

Forward Bending Sitting with feet apart and arms hanging loosely at sides bend the body forward until the head is between the knees (or above them) while breathing out and contracting only abdominal muscles The back should be rounded Then raise the body gradually pushing out the back and breathing in until the body is erect with the shoulders lowered the arms slightly drawn back and the back straight When beginning to breathe out relax the head forward first then the shoulders and the arms With small children small pieces of paper may be placed on the floor to be blown to encourage breathing out

Relaxing Exercise Sit with feet apart At first shrug shoulders slightly Relax shoulders and let arms hang heavily Later shrug shoulders and tighten arm muscles while pressing head back Then relax all muscles that were tense allowing head shoulders and back to sag

The next steps in the chain of rehabilitation proceed with the evaluation of the functional capacity of the lungs and readjustment to work

In evaluating the patient s chances for rehabilitation especially in intrinsic asthma an estimation of the functional capacity of the lungs and the patient s disability from a physiopathologic point of view should be undertaken This is an attempt at determining the

patient's total physical capacity The guiding physician should estimate the energy capacity of the patient It is known that the energy demands of many jobs are relatively low and in some jobs the demands do not exceed one to two times the resting oxygen consumption of the patient This determination involves pulmonary function studies

The determination of pulmonary functional capacity for which few physicians are equipped can be helped by the establishment of a lung station This is a laboratory designed to aid in diagnosis prognosis therapy and the evaluation of disability in pulmonary disease in much the same manner that a heart station serves the needs of clinicians concerned with heart diseases Such a lung station was demonstrated by pulmonary physiologists at a special exhibit on pulmonary function testing in June 1953 at the San Francisco meeting of the American Medical Association It is also important that the larger allergy clinics like the cardiac clinics establish work classification units

The most important step in rehabilitation is the readjustment to work Many patients are reluctant to go back to their former jobs since they often believe that their illness is a result of detrimental conditions of work A vocational counselor may be of utmost importance in this phase of rehabilitation It is his function to return the patient to a competitive productive life commensurate with the patient's abilities The problem consists in evaluating and matching the patient's capacity with the demands of a specific job (job evaluation technic)

The most important task that confronts the vocational counselor is placing an asthmatic in a job where he does not come in contact with offending allergens Unger has enumerated 38 occupations hazardous for the allergic patient The employes of these industries it was shown were exposed to no less than 144 effective allergens These occupations include bakers and millers sensitive to a variety of flours furriers sensitive to various animal epithelia and to chemicals and dyes mainly paraphenylenediamine used in the preparation of the furs pharmacists and chemists with drug sensitivity stable men and teamsters sensitive to animal epithelia and emanations laboratory workers hat makers rag sorters coffee handlers jewelry polishers barbers beauty parlor workers sawmill workers and woodworkers poultry farmers upholsterers sandblasters etc In some occupations such as the handling of raw and semifinished wool cotton kapok and cereal grains the patient is exposed not only to the primary allergen but to molds which may be present in such materials A baker sensitive to flour should be advised not to

look for a job in another bakery but to change his occupation altogether and avoid contact with the causative factor responsible for his allergy Atopic individuals in general should avoid industries which are associated with dust fumes sudden temperature variations smoke or irritating gases

In intrinsic asthma when the physical condition of the patient allows he should be rehired by his employer and given a chance to perform the work for which he is skilled possibly at first on a part time basis Should the readjustment fail a recommendation should then be made for job transfer within the plant With careful screening and placement in jobs for which they are physically and emotionally qualified a great number of asthmatics are capable of many valuable years of service without significant risk to their health The preemployment examination utilizing all modalities will certainly show what limitations should be placed on the employment of the chronic asthmatic In general he should be advised against heavy labor requiring pushing lifting and the carrying of heavy objects and should be utilized instead for lighter work such as time keeper or office worker Furthermore in this mechanized age many once arduous tasks can now be easily handled by the physically handicapped

Very little attention is given to disabled asthmatics although their number is high A civic group consisting of representatives of management physicians social workers and leaders in labor should initiate a Jobs for Asthmatics organization which could find work for thousands of asthmatics in fields of industry where they could work safely and adjust more satisfactorily to their health conditions In the experience of several cardiac work classification clinics 70 to 75 per cent of the cardiac patients have either shown no deterioration or have improved while working [8] If similar units to test classify and integrate asthmatic patients into industry existed it could be demonstrated that a high percentage of patients with bronchial asthma could be rehabilitated and returned to the status of wage earners According to data from the Physical Medicine and Rehabilitation Department of New York University-Bellevue Medical Center 90 per cent of the chronically ill and disabled patients derived some benefit from their rehabilitation experience

Under the guidance of a team consisting of a physician a social worker and a vocational counselor patients could improve their work tolerance and with proper medical help and emotional and supportive reassurance could maintain and improve their work productivity

The selective placement of asthmatics along with the proper cor

rection of their physical disabilities would open a new chapter in the history of rehabilitation The physician particularly the allergist should be the guiding force and cohesive influence throughout the total illness treatment and rehabilitation period of the patient

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ATOPIC DERMATITIS

Atopic dermatitis is among those common dermatoses which in most cases can be diagnosed without special dermatologic training A majority of physicians readily recognize the eruption in its three characteristic phases

1 In *infants* the lesions are eczematous (papulovesicular erythematous crusting and oozing) The principal localizations are the face and scalp with involvement frequently also on the trunk and the extensor aspects of the extremities

2 In *children* the lesions are lichenified thickened erythematous and papular The principal localizations are the flexor surfaces of the arms and legs the back of the neck and the wrists

3 In *adolescents* and *adults* the lesions are lichenified thickened and erythematous Unless secondarily eczematized as by irritating topical irritants features of eczema are lacking except on the hands and feet The principal localizations are the face neck scalp upper chest cubital spaces and wrists

Among the differential diagnostic possibilities eczematous contact dermatitis and seborrheic dermatitis are most important Differentiation between them and atopic dermatitis is usually not too difficult if the features listed in Table 22 are kept in mind

Much information is now available regarding the hereditary background as well as certain immunologic and nonimmunologic stigmata which are often encountered in patients with atopic dermatitis Most patients show one or more of the stigmata of the diathesis or hereditary tendency which is best called *atopy* (Coca) It is this

atopic background which is the feature common to the large majority of patients with the disease and which justifies the use of the name *atopic dermatitis* as a replacement for the older confusing or *misleading names such as disseminated* neurodermatitis and Besnier's prurigo Among the characteristics of the atopic diathesis is a familial tendency to allergic asthma allergic rhinitis atopic dermatitis and certain gastrointestinal and other disturbances wheal responses in skin tests with common food inhalant and contactant allergens presence of passive transfer antibodies in the blood serum tendency to blood eosinophilia tendency to anaphylactoid reactions to foreign serums penicillin etc

In a small minority of patients allergens (foods inhalants etc) can be shown clinically to contribute to the maintenance of the eruption and to produce flare ups These allergenic agents however must be discovered by subjecting the patients to *clinical* tests of

TABLE 22 DIFFERENTIAL DIAGNOSIS OF ATOPIC DERMATITIS CONTACT DERMATITIS AND SEBORRHEIC DERMATITIS

Diagnostic feature	Atopic dermatitis	Contact dermatitis	Seborrheic dermatitis
Localization	In typical areas (see characteristic phases listed in text) usually independent of detectable contributory factors	Mainly in areas of major exposure to the causal agent	In typical areas—scalp nasolabial postauricular axillary sternal and crural
Morphologic characteristics of lesions	Usually much thickening and lichenification with erythema eczematous (papulovesicular) lesions only in infants and very young children	Usually eczematous (erythematous papulovesicular) thickening and lichenification only in the chronic phase	Erythematous to brownish greasy scaly
Age groups involved	Any age but most common at ages 1 to 3 6 to 9 12 to 18 not common after age 25	Any age but most common at ages 20 to 50 relatively uncommon (except for plant dermatitis) before age 20	Any age but most common at ages from 20 years up
Familial tendency to seborrheic dermatitis and psoriasis	Usually not but seborrhea of scalp often present	Usually not	Often

TABLE 22 DIFFERENTIAL DIAGNOSIS OF ATOPIC DERMATITIS CONTACT DERMATITIS AND SEBORRHEIC DERMATITIS (*Continued*)

Diagnostic feature	Atopic dermatitis	Contact dermatitis	Seborrheic dermatitis
Familial or personal tendency to asthma seasonal rhinitis etc	Very common (about 80%)	Average (about 10%)	Average (about 10%)
Response to nonspecific therapy (exclusive of systemic steroid or ACTH therapy)	Often good even on a long term basis	Usually only moderately good or poor if exposure to specific etiologic agents continues	Often excellent
Tendency to white dermographism	Present	Absent	Absent
Tendency to blood eosinophilia	Present	Absent	Absent
Urticarial response in skin tests with protein food inhalant and contactant allergens	Often positive	Usually negative	
Eczematous reaction in patch tests with small molecular substances	Usually negative	Often positive	Usually negative

SOURCE Based on Sulzberger[1]

avoidance and reexposure since skin tests are not reliable as indicators of clinical sensitivity in atopic dermatitis

Certain other stigmata also are seen more or less frequently in patients with atopic dermatitis It is not yet known whether they are part of the mechanism underlying the disease or whether they develop as a consequence of it Among these are peculiar vascular responses (as shown by white dermographism * abnormal skin temperature responses and cold pressure responses and tendency to low blood pressure) flat blood sugar curves disturbances in sweating (probably an important factor in the severe itching because of self injected sweat and lack of cooling) susceptibility to secondary infection with herpes simplex virus and vaccinia virus (this may

* When the skin is lightly stroked—for example with the fingernail—a distinct white line develops instead of the usual red line

lead to death in infants) skin test reactions to human dander (the clinical significance of these is not yet clear) and cataract formation (fortunately very rare in mild cases)

Among factors which often have an unfavorable influence on the course of the disease are rapid changes in temperature emotional tension dusty environments alkaline cleansing agents including common toilet soaps contact with wool greasy topical medicaments and nonfebrile intercurrent infections (colds sinusitis) Diseases associated with high fever however often exert an evanescent beneficial action



Fig 30 1 Atopic dermatitis in nonidentical twin brothers sixteen years of age both of whom have had eczema since infancy Note the characteristic thickening lichenification erythema and evidences of scratching in the antecubital spaces and especially in the patient on the right on the upper chest and neck

Is atopic dermatitis due to a single etiologic mechanism? Or is it due to a combination of factors which are superimposed on a peculiar hereditary makeup and if so what is the relative importance of each of the various contributory mechanisms? The atopic hereditary background as well as the abnormal vascular responses and other stigmata mentioned indicate the very complex nature of the disease All the evidence available at present is against a single etiologic mechanism and favors a multiplicity of contributory factors which superimpose themselves on a peculiar terrain This is of

the greatest *practical* importance because obviously if there is no single major etiologic mechanism the sensible management of atopic dermatitis must be based on a combined approach rather than on a one sided attack It is likely that in the past the poor therapeutic results in many cases of atopic dermititis were due at least in part to just such one sided management of which purely allergic and purely psychosomatic approaches are outstanding examples

As already pointed out multiple positive skin reactions to protein food inhalant and other allergens are commonly seen in patients with atopic dermatitis It is an error however to manage such patients with diets and hyposensitization procedures based on the results of skin tests alone Only a small minority of atopic dermatitis patients in the author s experience can be reliably shown to be clinically sensitive to allergenic agents (Wool is a possible exception to this rule as discussed below) Even in those cases in which allergenic foods or inhalants have been shown to be contributory factors their elimination or avoidance *alone* while it may cause much improvement does not always lead to healing of the eruption

In those instances in which allergenic agents can be shown to contribute to the eruption foods are more often a significant factor in infants and young children inhalants in older children adolescents and adults Among the contactants wool is probably the most important single factor There are cases where a single wearing of a wool sweater even for a few hours is sufficient to produce a flareup in some of the exposed areas Whether the effect of contact with wool in many of these patients is due to an allergenic action or is the result of an irritating effect of the wool fibers on itch points or a combination of both has not yet been established

One sided management from the psychosomatic viewpoint in the author s experience has proved equally unsuccessful This is not surprising since there is no evidence that emotional difficulties play a major etiologic role Rather they are among the *many* links in the chain of factors contributing to the maintenance and flaring up of the disease It is obvious however that emotional tension is an unfavorable influence on any pruritic dermatosis and especially on one with the intense itching characteristic of atopic dermatitis

It would be surprising if a disease which if not successfully treated causes sleeplessness discomfort disfigurement and interference with the patient s normal social and economic development did not have a significant effect on the patient s psychic status and his relationship to his environment For example a child with severe atopic dermatitis requires and is likely to receive attention

from the parents far beyond that given to the healthy siblings More over the child is likely to utilize the dermatosis to arouse sympathy to obtain still more attention and to achieve objectives which are entirely unrelated to the disease Many physicians including the present author believe that these somatopsychic aspects of atopic dermatitis are generally probably *of much more importance* in these patients than the psychosomatic factors

MANAGEMENT

Treatment and prevention of recurrences in atopic dermatitis must be based on a consideration of *all* factors known to have an unfavorable influence on the disease together with measures which empirically have been found beneficial in many instances Obviously in mild cases of the disease it is unnecessary to take some of the steps *which are required in more severe ones The procedures which have* proved successful in the majority of cases may be summarized as follows

In mild cases

1 Topical therapy of a generally nonstaining greaseless and odorless type

a Triamcinolone acetonide or hydrocortisone preparations (creams lotions ointments)

b Antipruritic shake lotions—e g menthol 0 3 phenol 0 6 benzocaine 12 0 coal tar solution N F 6 0 resorcin 2 4 zinc oxide and talc each 20 0 glycerin 10 0 alcohol and water each 35 0 Paint on three or more times daily with 1 in flat varnish brush

c Medicated baths—e g Almay or Ar Ex tar solution for the bath 4 tablespoonfuls per bath or coal tar solution N F or Zetar for the bath 2 tablespoonfuls per bath

d Antiseborrheic treatment for the scalp—e g Selsun Suspension twice weekly for two weeks and then once weekly

e Avoidance of greasy topical medicaments (exceptions triamcinolone acetonide and hydrocortisone ointments)

2 Systemic antipruritic therapy with

a Antihistamines—e g Teldrin 12 mg after breakfast and Phenergan 12 5 to 25 mg after dinner

b Thorazine 25 mg three to four times daily

c Aspirin 0 3 Gm four times daily (avoid in cases associated *with asthma*)

d Papaverine hydrochloride 0 1 Gm four times daily

3 Substitution of a mild soapless detergent bar for toilet soap—e g Dove bar or Lowila Cake
4 Avoidance of exposure to persons with herpes simplex lesions

In more severe cases add

1 Topical therapy if necessary of a less convenient type (including some remedies which stain and require bandaging) For example

a Hydrocortisone powder 0 3 crude coal tar 0 6 Sterosan ointment 30 0 Apply lightly to affected areas three times daily

b Hydrocortisone powder 0 3 crude coal tar 3 0 paste of zinc oxide 30 0 Apply in thick layer to affected areas cover with muslin material and bandage

2 Avoidance of allergenic agents clearly suggested by the history
3 Radiation therapy (grenz rays superficial x rays)
4 Avoidance of direct contact with wool
5 Avoidance of activities producing sweating or rapid changes in temperature
6 Avoidance of emotional stress
7 Avoidance of dusty environments

If no significant improvement occurs after four weeks of such management

8 Careful study for possible allergenic factors by avoidance and reexposure tests and in some cases by skin tests
9 Hospitalization for two to three weeks

In otherwise intractable cases add

1 Systemic therapy with dexamethasone triamcinolone methyl prednisolone prednisone or ACTH first in suppressive doses and subsequently in minimum maintenance doses In many cases this has to be continued for many months or years unless it is used on a short term basis only for suppression of an acute exacerbation of short duration Do not rely simply on such treatment but combine with the other measures listed above (see Chap 34)

2 Complete change in environment preferably to a dry warm climate for a period of weeks months or years

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31

Aaron D Spielman

URTICARIA AND ANGIOEDEMA

Urticaria and angioedema belong to the group of skin diseases known as allergic dermatoses These dermatoses have been grouped together because of their common allergic etiology The allergic dermatoses include in addition to urticaria and angioedema which are relatively common diseases the less common manifestations of purpura and erythema the latter well illustrated by erythema multiforme Osler in the early 1900s called attention to the frequent association of these diseases with visceral lesions He predicted that a common cause would be found for these diseases probably hypersensitivity

Hypersensitivity has been increasingly recognized since Osler's prediction as the probable basis for this entire group Many of the patients have a family and personal history of allergy Most of them have been made ill by very similar causes an allergic reaction to a drug or food or the presence of infection Moreover it is quite common *to see in the same patient lesions of several of the allergic* dermatoses at the same time with complications in any one of them involving the gastrointestinal tract the kidneys and the joints

That urticaria is a common disease is unappreciated since it is frequently mild and disappears rapidly Its frequency was clearly demonstrated by Sheldon and his colleagues[1] who found that 15 7 per cent of 1 424 college students had had at least one bout of hives Swinny[2] likewise showed that in a group of 1 000 patients studied the incidence of urticaria was 23 6 per cent and a history of urticaria

was almost two and one half times as common in patients who had had asthma or hay fever as in those who had not

CLINICAL APPEARANCE

Urticaria frequently must be differentiated from the lesions of the erythema group such as erythema multiforme In urticaria the itching is much more marked while in erythema the lesion is more persistent and often painful



Fig. 31 1 Urticaria of back with large and small wheals

Urticaria (Fig 31 1) may be confused with urticaria factitia or dermographia (Fig 31 2) In the latter condition the wheals occur on areas of friction or pressure as where garters or belts are worn and even stroking the skin will produce whealing thus establishing the differential diagnosis

Wheals the typical lesion of urticaria have several easily recognizable characteristics They vary in size are surrounded by a zone of erythema and itch intensely They may be present over only a small area or over the entire body In acute urticaria they tend to disappear even as new wheals are erupting in chronic urticaria they recur periodically and may last for hours or days

The lesion of angioedema involves chiefly the eyes tongue lips hands feet and larynx This lesion because it originates in the deeper subcutaneous tissues of the skin shows greater edema and is less circumscribed and defined than the urticarial wheal Itching is not so pronounced and there is a stinging and burning sensation instead Attacks of angioedema may last from one to four days and *are likely to recur at irregular intervals When the larynx is in*



Fig 31 2 Dermographia

volved the patient may be in danger of strangulation (see Chap 61) Unlike other forms of edema angioedema is not dependent or symmetrical The tendency to frequent involvement of the face lip tongue or one hand distinguishes it quickly from the numerous other types of edema (Fig 31 3) Eosinophilia is usually absent in angioedema and urticaria

Elephantiasis nostras a chronic low grade streptococcic lymphangitis can be confused with angioedema especially when it occurs about the nose or lips and is followed by a red swelling This swell

ing unlike angioedema remains for weeks or months causes a fever and responds well to antibiotic therapy



Fig 31 3 Angioedema of lower lip

HISTOPATHOLOGY

The lesion of urticaria involves the upper papillary layer of the cutis whereas in angioedema the deeper subcutaneous tissue is involved The urticarial wheal is characterized mainly by exudation of serum This exudation of serum through the capillary wall follows a dilatation of the capillaries in the cutis In angioedema the arterioles as well as the capillaries become dilated causing greater exudation Because of this the lesion of angioedema is larger and less localized particularly at a mucocutaneous junction (see Chap 10)

It is generally accepted that the pathology of urticaria and angioedema is based on the liberation of histamine or an H substance at the affected site This is a *completely* reversible reaction Proof of the histamine theory is based on the elicitation of a similar response on injection of histamine into the skin and also on the ability of antihistaminic drugs to inhibit the production of this lesion by injection of histamine or of allergens such as pollens

Recent studies[3] *strongly indicate that the autonomic nervous system* and acetylcholine may also be involved In cases of urticaria due to heat exercise and stress there is evidence that the central nervous system initiates impulses which are sent to the skin through the autonomic nervous system and these are followed by the release of acetylcholine The latter *in some manner not yet entirely clear* causes the production of urticaria Some *investigators* state that the

release of acetylcholine is in turn followed by the release of histamine which actually is the cause of the urticarial wheals If this is so the reason for the relief seen in such cases with the use of antihistamines becomes readily apparent

ETIOLOGY

The basic factor in the majority of patients with urticaria is the presence of an allergic constitution Almost 50 per cent give a family and/or personal history of allergy The main etiologic factors in urticaria and angioedema are drugs foods and foci of infection in that order of importance Emotional stress and other psychogenic factors undoubtedly play an important role Patients develop urticaria in a setting of emotional stress They also have persistence of urticaria under emotional stress long after the *specific antigen* has been eliminated While it is difficult to prove that urticaria may have a purely emotional etiologic basis often enough the evidence strongly favors such a conclusion

The existence of a purely emotional etiologic basis for urticaria is born out by Graham s work [6] He has been able to show that during periods of resentment arterioles and minute vessels dilate This in turn leads to a transudation of fluid with the appearance of edema or hives He further shows that when the skin is already in such a condition of increased sensitivity many nonspecific agents may become factors in the development of these dermatoses Under these conditions the skin becomes more sensitive to chemical agents so that lesser amounts of histamine which under one set of circumstances and emotions produce no reaction under others may cause urticaria

The role of food allergy may have been overemphasized In the period prior to the antibiotic age food allergy was suspected in about one third of the cases of urticaria and angioedema but proof of such a relationship could be elicited in only 15 per cent Since the advent of the antibiotic age the incidence of drug urticarial reactions has increased tremendously and this increase to a great degree has been due to the use of penicillin Indeed many allergists feel that drug reactions probably account for more than 50 per cent of the cases of urticaria (see Chaps 46 47 61)

There are numerous other causes of urticaria and angioedema They are inhalants such as pollens or animal danders contactants such as wool nylon or animal saliva physical agents such as cold heat ultraviolet light and exercise endocrine products and insect

Max Grolnick

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OCCUPATIONAL CONTACT DERMATITIS

Occupational contact dermatitis is variously referred to as allergic dermatitis, contact dermatitis, dermatitis venenata, eczema, and allergic eczematous contact dermatitis of occupational or industrial origin.

Contact dermatitis is of such concern in daily life and in industry especially that in 1928 the Public Health Service organized the Office of Dermatoses Investigation for the study of occupational and other forms of contact dermatoses. Furthermore, occupational dermatoses are of such importance as to be covered by the compensation laws of most of our states, being considered as occupational diseases.

The estimate by various sources of the incidence of occupational dermatoses is from 2 to 20 per cent of all skin diseases.[1]

While it is necessary to understand the principles governing sensitization of the skin under the usual conditions of living, it is even more important to be able to evaluate them in relation to industry and commerce. In interpreting the action of a substance on the skin one must distinguish between a primary irritant substance, which produces its effect by direct action (physical and/or chemical) on the skin at the site of contact from single or prolonged exposures (Fig. 32.1) and a sensitizing excitant, which by single (rarely) o[illegible] peated exposures may cause the entire skin surface to becom[illegible] a[illegible] lergic or sensitive to it. Sensitization is brought about by [illegible] immunologic (specific) effects, so that further contacts at th[illegible] [illegible] or other areas will produce a characteristic dermatitis. O[illegible] [illegible] then state that the sensitized skin has developed a specifi[illegible] [illegible] capacity to react, induced by previous exposure to a poten[illegible] [illegible]

and reproduced by subsequent exposure to the same (or a closely related) excitant

SENSITIZATION OF THE SKIN

The Sensitizing Substance The importance of a specifically active substance was stressed by Bloch who also demonstrated the effect of



Fig 32 1 A nonspecific (nonallergic) dermatitis due to a seven-day contact with adhesive tape

the concentration of the excitant When the human skin was treated locally with a dilute preparation of primula extract from the prim rose only 42 per cent of the *subjects were sensitized* The use of a concentrated extract was effective in sensitizing all subjects to it The strength of the excitant also influenced the time of appearance of sensitization Thus when Silverberg[3] treated an area of skin in

human subjects with daily unction of a 10 per cent ointment of mesotan (a salicylic ester) sensitivity appeared in from twenty to twenty five days When a 100 per cent ointment was employed sensitivity occurred in from seven to ten days

It is believed by most investigators that a good sensitizing agent must be a primary irritant in high concentration Landsteiner and Jacobs[4] asserted that most substances capable of sensitizing were in



Fig 32 2 Subject in whom sensitization was induced by two patch test applications of the excitant *Krameria*

(B) Spontaneous flare up at site treated first (C) Reaction at site treated last

themselves irritating although such an effective excitant as para phenylenediamine (a dye) had little primary action on the skin and some irritating chemicals were incapable of inducing sensitization

To establish the role of an excitant as the cause of a dermatitis there must have been adequate exposure of the subject to it On initial contact of newborn infants with a tiny amount (patch test)

of a strong poison ivy extract Straus[5] failed to find evidence of any skin reactions but on subsequent testing several weeks later there were positive reactions in 73 per cent Grolnick[6] found a reaction incidence of less than 1 per cent in human subjects tested with a strong extract of *Krameria* (a plant substance) but sensitization was achieved in 90 per cent of subjects by appropriate technics (Fig 32 2)

In industry the skin may be injured nonspecifically from the exposure to or handling of liquids oils lubricants solvents gases and vapors or dusts Such skin reactions must be distinguished from those mediated by an immunologic mechanism It must further be kept in mind that a nonspecific dermatitis may be aggravated and prolonged by a superimposed sensitization due to contact with other substances to which the subject has been exposed in his daily living or even by the application of local medications intended to correct the dermatitis

The various groups of substances which can sensitize the skin either in daily living or in industry may be classified as shown in Table 23

TABLE 23 CLASSIFICATION OF CONTACT ALLERGENS

1 Botanical group
  a Plants
  b Woods
  c Fruits and vegetables
2 Cosmetic group
  a Hair dyes
  b Hair tonics and shampoos
  c Creams
  d Rouges and lipsticks
  e Mouth washes and dentrifices
  f Perfumes and toilet waters
  g Powders
  h Deodorants
3 Dyes
  a Cosmetic group
  b Clothing
  c Fur
  d Leather
  e Inks and stains
4 Soaps and washing materials
5 Clothing materials
  a Textiles
  b Animal substances
6 Metals
7 Drugs
  a Anesthetics
  b Antiseptics
  c Alkaloids
  d Miscellaneous
8 Insecticides and parasiticides
9 Oils resins and related substances
  a Adhesive plaster
  b Lacquers
  c Essential oils and oleoresins
  d Paints and accessories
  e Synthetic resins
  f Polishes
10 Rubber compounds
11 Industrial chemicals
12 Miscellaneous

Susceptibility of the Subject This might be defined as the individual s capacity for becoming sensitized and signifies the extent to which sensitization can be induced under favorable circumstances

in subjects not previously exposed to the excitant That it varies with different excitants is evident from experimental studies which indicate the percentage of subjects who could be sensitized to various substances by appropriate technics as follows primula extract 100 per cent dinitrochlorobenzene 70 per cent [7] poison ivy 73 per cent [5] orthoform 45 per cent [8] krameria 87 per cent [9]

Experimentally there is a distinct individual variation in sus ceptibility to sensitization Of 37 subjects sensitized by from one to five patch test applications of krameria repeated at weekly intervals 18 required one test 8 needed two 6 had three 4 had four and 1 required five such contacts [9] Individual variations in developing sensitization were likewise shown by Sulzberger and Rostenberg [10] who demonstrated also that subjects with recent or active contact dermatitis were more readily sensitized than control subjects

The influence of the atopic mechanism in allergic contact der matitis has not been established Brown Milford and Coca [11] de monstrated that sensitivity to ragweed oil occurred with equal fre quency in both atopic and nonatopic persons Schwartz [1] found that a personal or family history of atopic diseases was not preponderantly present in those affected with industrial dermatitis

The Incubation Period This is the time involved in the develop ment of the *spontaneous flare up reaction*—the first visible evidence that a subject previously nonsensitive has developed a state of hy persensitiveness (allergy) The term was used by Frei [13] to describe the spontaneous appearance (*Aufflamungsphanomen*) in man of deep inflammatory reactions at the sites of intracutaneous tests with Neosalvarsan introduced eleven to twelve days previously The flare up signifies the culmination of those immunologic processes which have been stimulated by the primary exposure

This flare up phenomenon has been reported by many observers as a manifestation of acquired allergy (contact type) of the skin Where a single simple contact on a small area was effective in sen sitizing the subject there has been found a striking uniformity in the limits of the incubation period i e from seven to twenty four days regardless of the allergenic substance employed or its manner of application Wedroff and Dolgoff demonstrated a range of eight to twenty four days for dinitrochlorobenzene For this chem ical and for p nitrosodimethylaniline the incubation periods were shown by Sulzberger and Rostenberg [10] to be from seven to twenty days Straus [14] reported the onset of sensitivity in the monkey seven to ten days after the simple patch test application with poison ivy extract The incubation period for krameria in human subjects was eight to twenty-one days [9]

When sensitization procedures other than a single contact were employed experimentally the range of the sensitization period be came less uniform longer intervals being observed This is probably what occurs in industry and commerce The individual receives multiple exposures at regular or irregular intervals At some time in this sequence the immunizing process (sensitization) starts and the person becomes sensitized within the incubation period established for that particular substance

Once sensitization has taken place there is a change in the response of the skin It no longer waits for the usual incubation period but reacts on suitable contact (tests) in from twenty four to forty eight hours and not infrequently within the first twenty four hours This is the *reaction time* and must be distinguished from the incubation period [15] The response of the skin of the sensitized individual within *this shortened period forms the basis for performing the conventional* diagnostic patch test the test substances being applied for twenty four to forty eight hours

DIAGNOSIS

History A detailed careful history can be most revealing Such information should be elicited as for example the total period of employment any recent change in work procedure or materials the effect on the eruption of a sustained period away from work the direction of spread of the dermatitis etc It is essential too that con tacts other than those encountered at work be ruled out as possible causes of the dermatitis such as household excitants hobby materials cosmetics and medicaments used locally or systemically

Examination Inspection of the lesions will suggest the acuteness or chronicity of the dermatitis The location of the lesions will gives clues as to etiologic possibilities at the employee s place of work and will help to rule out sources of contact encountered away from work

Patch Test The purpose of the patch test is the reproduction of the skin lesion seen clinically on an uninvolved area of skin *It* represents a delayed type of allergic response the reaction occuring generally within the first forty eight hours The concentration of the excitant must be nonirritating so that a primary burn is not produced and reported as indicating a sensitivity reaction Standard lists of proved nonirritating concentrations of known excitants are available to those who wish to use this diagnostic procedure in telligently and safely It must be realized too that a patch test with some excitants in fairly high concentrations although not neces

sarily in an irritating strength or repeated patch tests with some excitants in nonirritating concentration may cause sensitization of the general body surface It is not improbable that when some diagnostic patch tests are repeated because the results are negative or doubtful the repetition with the same or related allergens may actively sensitize the patient to the substance being applied Such practices should be discouraged [16]

One other hazard of the patch test should be pointed out The application of the specific substance during the active phase of a localized dermatitis may cause a general spreading of the process It is also possible to effect a recurrence of a healed dermatitis by the patch test application of the specific causative substance

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Albert M Kligman

POISON IVY (RHUS) DERMATITIS

McNair s wonderful little book *Rhus Dermatitis* is the most complete treatment of the subject in it knowledge is summarized up to 1923 [1] The modern master is Bedford Shelmire his original studies are impressive examples of biological research at the clinical level [7] Exclusive of biochemical accomplishments the remaining literature is excessively preoccupied with prophylaxis and therapy the yield therefrom is not in proportion to the number of papers

The objective of this chapter is to draw together current information to present new data on Rhus sensitization and to deal with the problem of hyposensitization * The problems shed light on the general subject of allergic contact dermatitis of which poison ivy dermatitis is merely a species

BOTANY

The family Anacardiaceae includes many widely distributed species both noxious and useful The baleful species of which certain members of the genus Rhus have achieved notoriety in the United States have in common the capacity to induce a severe contact dermatitis All the dermatitogenic Anacardiaceae are members of an immunologic cross reacting group owing to biochemical similarities

* Dr William Epstein participated in the field studies on soldier personnel at Fort Ord Calif and Dr Joseph Corcoran on the inmates at the Philadelphia County Prison Holmesburg Pa The younger subjects were retarded children in the New Jersey State Colony at Woodbine

of their antigens Sensitization to one carries with it the verdict of allergic reactivity to the rest (see Appendix III)

Each of the following dermatitis producing Anacardiaceae also possesses some agreeable or economically useful property (1) Rhus verniciflua the lacquer tree from which Orientals prepare a rich furniture lacquer (2) Semecarpus anacardium the India ink tree or marking nut used to stain clothing often as a laundry mark (3) Mangifera indica the mango a delicious fruit (4) Anacardium occidentale the cashew nut an oil is obtained from the shell which is valuable in resin manufacture the meat of the nut is a favorite delicacy the world over (A further description of the Rhus plants and their distribution can be found in Appendix III)

Rhus species are by far the Number One cause of allergic contact dermatitis in the United States the sufferers from which exceed in number the total of all other forms of allergic disease combined

Many *other species* of unrelated plants may also cause allergic contact sensitivity McNair [1] provides a lengthy list and Shelmire [2] has studied the problem specifically in the southwestern United States None of these diverse plants can match Rhus species in allergenic potency with the consequence that only occasional persons having a special predisposition and probably intensive contact ever become sensitized Still recognition of this problem is quite important for *I have encountered several persons who had received* prophylactic injections against Rhus dermatitis when in fact other plants were at fault!

CHEMISTRY

The peak achievement in studies relating to poison ivy dermatitis has been the chemical identification of the allergenic constituents of the plant These are precisely known mainly through the splendid researches of Dawson and his collaborators of Columbia University the world center of Rhus biochemistry [9] Dawson [10] has recently traced out the evolution of biochemical knowledge in a remarkably interesting essay which takes pains to render the chemistry understandable to the educated nonexpert

The salient findings of the Columbia researchers [10, 11] with poison ivy may be summarized as follows There are four antigenic components These are all 1 2 dihydroxy benzenes (catechols) with a 15-carbon atom side chain in the 3 position The only difference among the four antigens is the degree of unsaturation of the side chain The saturated component (hydrourushiol) illustrates the general structure (Fig 33 1) The other three antigens are a monoolefin (one unsaturated bond) a diolefin (two unsaturated bonds)

and a triolefin Table 24 indicates the approximate proportions of the four antigens and the location of the double bonds and contrasts the findings with Japanese lac[10, 18, 19] All are insoluble in water

The saturated component 3 pentadecylcatechol (hereinafter called PDC) was first synthesized in crystalline form at Columbia[0] in 1944 and shortly afterward by Mason[1] It is the minor antigenic component in both poison ivy and Japanese lac Being saturated it is more stable but at the same time less chemically reactive than the unsaturated catechols Its synthesis is more readily accomplished than synthesis of the olefinic components and limited quantities have been made available for clinical studies Keil[*] has investigated its effectiveness in the treatment and prophylaxis of poison ivy dermatitis *He*[3, 4] and his collaborators have found that poison ivy sensitive patients will uniformly react to patch tests with 1 0 and 0 1 per cent concentrations of PDC in acetone It is superior to the variable crude plant extracts for routine epidemiologic patch testing

TABLE 21 PROPORTIONS AND LOCATION OF DOUBLE BONDS OF ANTIGEN IN POISON IVY AND IN JAPANESE LAC

Component	Side chain	Poison ivy App % composition	Poison ivy Position of unsaturated bonds	Japanese lac App % composition	Japanese lac Position of unsaturated bonds
Saturated	$C_{15}H_{31}$	3		5	
Mono olefin	$C_{15}H_{29}$	20	8	25	8
Diolefin	$C_{15}H_{27}$	55	8 11	15	8 11
Triolefin	$C_{15}H_{25}$	22	8 11 14	55	8 11 13

Relationship Between Chemical Structure and Immunobiologic Activity By patch testing poison ivy sensitive patients with various synthetic phenolic derivatives Keil and his coworkers[3] have worked out the general structural requirements for cross reactivity and have come to the following conclusions

1 The presence of free phenolic groups confers high dermatitis producing powers

2 The position of the side chain and its length are highly significant Cross reactivity is most intense when the side chain is in the 3 position 4 pentadecylcatechol is less active than 3 pentadecyl

catechol Longer side chains have greater allergic activity For instance a 15 carbon atom side chain as in 3 pentadecylcatechol is considerably more active than 3 methylcatechol in which the side chain is reduced to a single carbon atom It should be noted however that a few mild cross reactions occurred to catechol itself which has no side chain

3 Unsaturated side chains confer higher biologic activity

A comparison between saturated PDC and a crude poison ivy extract (principally a mixture of olefins) has been made by me Quantitative patch testing of a group of 11 poison ivy sensitive subjects

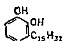


Fig 33 1 3 pentadecylcatechol (hydrourushiol)

with serial 10 fold dilutions in acetone showed that weight for weight the titer (greatest dilution still giving a reaction) of the natural oil was generally ten times (one dilution) greater than the saturated synthetic PDC this despite the fact that probably less than 50 per cent of the ether extracted natural oil (urushiol) is truly antigenic[25] The higher activity of the natural antigens may be reasonably ascribed to the preponderance of olefins It should be emphasized however that the potency of plant extracts varies enormously

CLINICOBIOLOGY

The dermatitogenic plant sap is distributed via a widespread system of resin canals situated in the roots stems leaves and fruit Portions of the plant which lack these namely the anthers pollen xylem and epidermis are unable to cause a dermititis The resin canals do not connect to the surface and there are no glandular appendages as in many other dermatitis producing plants The consequence is that the leaf must be bruised to produce a dermatitis Uninjured leaves are completely innocuous Shelmire[3] has justifiably accented this point Since exposure to the plants is not consistently followed by a dermatitis the disorder often seems capricious this is the basis for scores of worthless prophylactic prescriptions as well as numerous lay fallacies I placed fresh intact leaves on the forearms of six highly sensitive subjects who carefully wore the

leaves under a soft cotton dressing for 12 hours In each instance a tiny spot of dermatitis developed at the cut end of the leaf stem and in three a few tiny vesicles developed directly under the leaves presumably from inadvertent injury Several patients who considered themselves immune were dispossessed of this belief when I vigorously rubbed leaves on their skin their sensitivity was low but definite The degree of exposure is most important Mildly sensitive persons can probably withstand average casual exposures to the plant without difficulty

When the plant is cut a milky sap exudes this shortly turns into a black varnish which permits the economical use of the marking nut tree (laundry mark) and Japanese lacquer McNair[1] thought that the dermatitogenic property was lost after this change but I have found that if drops of sap are placed on slides allowed to dry and to turn black and kept in a desiccator they can still cause a dermatitis a half a year later Similarly Shelmire[31] found that blackening of the sap did not render it inert In a moist chamber however the droplets will completely lose their dermatitogenic activity within a week Moisture promotes degradation Shelmire[7] found that extracts containing as little as 5 per cent water deteriorated rapidly McNair[1] proved that the blackening was due to the presence of an oxidase which requires both oxygen and moisture for its effect Sizer and Prokesch[3] found that mushroom tyrosinase would catalyze the oxidation of Rhus antigens with a concomitant loss of dermatitogenicity The chemistry of oxidation is poorly understood and the question of whether oxidation alone can render the antigens inert is still sub judice

The term *oleoresin* refers to the crude yellowish brown viscous residue remaining after evaporation of solvents (ether alcohol acetone) used to extract the plant Loev estimates by chemical ayalysis that the lesser portion of the oleoresin is catecholic or truly antigenic material

Testing with extracts (oleoresins) is not at all comparable to the use of the fresh plant The extraction procedure markedly affects the potency Shelmire[5] states that alcoholic extracts are less active than ether extracts and that extracts made from fresh plants are more antigenic but deteriorate more rapidly than those from dried leaves To overcome this Spain and Cooke[34] recommended that the leaves be dried before extraction Standardization is much needed but difficult The use of pure synthetic antigens has obvious advantages

Fresh green leaves kept in the refrigerator in a sealed wet jar maintained almost their full dermatitogenic strength for about two months and thereafter gradually deteriorated becoming moldy

and impotent in about six months Curiously enough the allergenicity of the leaves diminished even more rapidly in sealed envelopes in the deep freeze the degradation may not always be enzymatic

The peak incidence of poison ivy dermatitis in the springtime cannot be ascribed to increased virulence of the sap Factors of probable significance are that (1) being more tender the leaves are more readily bruised in late summer especially in hot sunny locations the leaves are quite tough and leathery (2) the call of the outdoors is never so strong as in spring for many this is the only time of year when the urge to commune is irresistible (3) the strongly sensitive become more wary as the summer progresses (4) the possibility of desensitization or hardening with repeated attacks may be mentioned but is probably remote under ordinary circumstances

Many persons insist that they can acquire poison ivy dermatitis by merely being in the vicinity of the plants and some indeed do so without even being near them That there are gaseous emanations is folk myth The antigenic components are nonvolatile and filtered smoke is harmless but not if it contains plant particles However direct contact with the plant is not a prerequisite for the dermatitis The dermatitogenic sap may be transmitted via many intermediate fomites such as fingers shoes clothing tools domestic animals etc *

The following experiments explored this question further Various types of cloth (silk cotton rayon nylon) shoe leather and flat pieces of wood were contaminated by rubbing them with leaves At 37 C in the incubator under conditions of 100 per cent humidity the dermatitogenic power had practically disappeared within three to five days when the various articles freshly moistened were applied to highly sensitive skin During the hot humid weather of the Philadelphia summer the articles became inert in a week when left exposed on a table On the other hand after a week in the desiccator at room temperature the articles could initiate a brisk dermatitis and this capacity was retained to a lesser extent nine months later Evidently when the articles are dry the antigenic principles contained in the sap may last indefinitely A few days under moist warm conditions causes rapid deterioration of the antigenic film on clothing or objects Sap-contaminated clothing was rendered

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* The most interesting case in my repertory was an elderly woman who suffered the dermatitis continuously throughout the summer without leaving her house Her dog a frisky boxer visited the surrounding woods daily An ether soaked wad of cotton rubbed over the dog s coat gave a markedly positive patch test reaction in another sensitive subject

harmless after washing in an automatic laundering machine using soap flakes or a commercial detergent

Possessed of the true scientific spirit Shelmire[5] deliberately contaminated his hands with crushed leaves one morning washing thoroughly five minutes later During the day s practice six persons acquired a dermatitis for which the term *contact* is most appropriate Exceedingly small quantities of the antigen on the hands or other objects will excite a dermatitis in a highly sensitive person This is the probable reason that the dermatitis may continue to develop in different areas for a period of days after one exposure It has been repeatedly demonstrated that the blister fluid contains no antigen[8,35] the common belief that the disease spreads through rupturing of the vesicles is without merit However there is partial truth in the notion that the disease may be spread through scratching or is in the loose sense of the term contagious It is the antigen of course which is transmissible

The degree to which the antigen survives on the skin is a point of some interest I rubbed leaves on the backs of two nonsensitive persons covering the contaminated areas with perforated plastic cups Daily thereafter a moistened thumb was pressed against the contaminated spots and immediately applied with a firm twisting motion to the forearms of two highly sensitive subjects For three days but not thereafter the dermatitogenic principle persisted in sufficient quantity to excite a dermatitis but barely so after the second day In summertime deterioration of the antigen on the skin is rather rapid an effect in which surface moisture doubtlessly plays a role This plus its natural loss or removal limits the time that contaminated skin can be a vector for the antigen s dispersal Occasionally in highly sensitive patients a patch of weeping bullous dermatitis will appear to enlarge peripherally The bullae of course contain no antigen but after rupture the free fluid could conceivably become contaminated with residual surface antigen

Residues on freshly contaminated skin especially the hands have an astonishing capacity to excite new areas of dermatitis by contact The frequency of the dermatitis on the face genitals and covered areas in highly sensitive patients testifies to this This property is highlighted by the following demonstration The thumb of a nonsensitive person was contaminated by the juices of fresh leaves It was then pressed down on the back of a nonsensitive subject 500 times consecutively each time firmly Every 100th thumb print was made on the moistened forearm of an exquisitely sensitive person The 500th print evoked a mild dermatitis! The most sensitive subject I have encountered reacted to 0 25 ml of 1 50 000 000

PDC in acetone (the highest dilution tried). A dermatitis resulted in this person after contact with contaminated hands which had subsequently been scrubbed with soap and water for five minutes. Thus the minutest traces of sap will cause a dermatitis in highly sensitive persons. Generalized eruptions come about in this manner. The extraordinary hypersensitivity of some persons seems all the more extreme when it is recalled that probably only a small percentage of what is deposited on the surface actually penetrates into the skin.

Shelmire[4] recognizes two types of poison ivy dermatitis: (1) the allergic and (2) primary irritant. According to him, the milky fluid is as escharotic as phenol, and all persons who contact the sap acquire a dermatitis. I cannot concur in this, having applied root, stem, and leaf sap without harm to nonsensitive persons. Surely from the clinical standpoint, poison ivy dermatitis is primarily an allergic disorder.

The toxicity of the plant when eaten has received some attention. McNair[1] cites a number of authors who witnessed severe internal poisoning in persons chewing the leaves to gain immunity and also in children who had eaten the fruit. Prominent symptoms were drowsiness, convulsions, nausea, and vomiting. One case terminated fatally. Since these unfortunates were usually sensitive, the question arises as to whether the noxious effects were expressions of allergy to the catechol antigens, to unrelated toxins, or to both acting together. Inadequate documentation of most of these cases, which nowadays are rare, makes analysis of the cause difficult. However, the rapid onset of gastrointestinal reactions is against an allergic origin. The plant sap may very well contain toxic substances which are totally unrelated to the antigenic content. There is no question that the administration of a large antigenic dose to a highly sensitive person can produce severe systemic reactions on an allergic basis (see below).

I gave by mouth 1 oz. of a 25 per cent sesame oil solution of oleoresin (not sap) to five nonsensitive subjects. Only one person experienced a mild gastrointestinal upset. When the solution was applied to the skin by patch test, one of eight nonsensitive persons gave a questionable reaction (was he mildly allergic?).

INNATE IMMUNITY AND SENSITIZABILITY

Uncontrolled and uncritical observations, abetted by folklore testimonies, have considerably confounded the question of susceptibility. For instance, it has been widely rumored that full-blooded In-

dians are immune yet by patch testing with concentrated oleoresin Deibert and his associates[36] uncovered a sensitivity incidence of 56 per cent in full blooded Indians as compared with 58 per cent in whites One is always encountering persons who boast of their immunity Some of these are merely weakly sensitized Casual exposure does them no harm I have demonstrated this a number of times by *producing a mild dermatitis in such claimants by vigorously* crushing leaves on their skin Among students Brown[37] found practically none who did not react to leaves including those who claimed immunity Others who flaunt their resistance are brought to grief later when to their astonishment often following some exhibitionistic act of chewing or crushing the leaves they suddenly find themselves sensitive sometimes severely so Two of the worst cases of poison ivy dermatitis I have ever seen were in college students who on a dare anointed themselves with crushed leaves Some persons with evident opportunities for prior exposure do not become sensitized until adult life It is well known clinically that sensitizability varies markedly not only among persons but even in different periods of the same person s life Inexplicably a patient may handle a potentially allergenic substance innocuously for decades before becoming sensitized Heredity doubtlessly plays some role in sensitizability but is of minor importance with highly potent allergens As an illustration practically everyone can be sensitized to dinitrochlorobenzene[38] Rhus antigens are in the same class

Against the evidences of supposed innate or acquired immunity to Rhus antigens stand the far more substantial objective findings which follow

Newborn infants are not Rhus sensitive By a single topical application of a poison ivy paste Straus[41] sensitized 73 per cent of 119 newborn infants After a single application of 0 25 ml of 1 per cent to 3 per cent PDC in acetone I sensitized about 85 per cent of 34 young children between the ages of two and eight who could be presumed not to have been previously exposed Most impressive of all is Biberstein s[4] demonstration that practically 100 per cent of a previously unexposed European population could be experimentally sensitized by application of leaves or the oleoresin! Previous nonexposure is a factor of crucial importance

The conclusion is inescapable that under controlled conditions when the time and quality of the antigenic exposure are known sensitization to Rhus antigens takes place readily In America the great majority of the population becomes sensitized merely by casual contact with the plants Mere traces of allergen are sufficient It is probably unwise to assume complete resistance to sensitization in anyone *Cave Rhus!*

There is no relationship between immediate type allergy (atopic allergy) and the liability to allergic contact sensitization Knowles *et al*[43] did not find a higher rate of Rhus sensitivity among those with a family history of asthma hay fever urticaria vasomotor rhinitis eczema and migraine

INCIDENCE

The epidemiologic figures obtained by patch testing and compiling of clinical cases of Rhus dermatitis have no exact meaning There are too many variables some of which are altogether unknown viz time of first exposure degree and frequency of exposure etc The percentage of reactors at any given time in a random sample is influenced by age occupation geographic location personal habits genetic constitution race and other variables

TABLE 23 INCIDENCE OF LEAF REACTORS

Place	Race or national origin	Incidence	Percent with positive history
California	White	493/80[illegible] (53%)	
	Negro	1[illegible]/53 (3[illegible] %)	
	Puerto Rican	2[illegible]/89 (28%)	33%
	Hawaiian	10/21 (4[illegible]%)	
Philadelphia †	White	[illegible]3/416 (54%)	
	Negro	383/9[illegible] (4[illegible]%)	48%

Soldiers at Fort Ord These men originated from all over America Hawaii and Puerto Rico Poison oak grows in incredible profusion in this area of California The actual sensitizations of course may have arisen elsewhere

† Inmates of Holmesburg Prison Most of these men had spent their lives in the East and were short term inmates

The incidence of sensitization given by various authors is as follows Spain *et al* 60 per cent (adults reactive to oleoresin)[44] Knowles *et al* 50 per cent (young adults reactive to dried leaves)[43] Diebert *et al* approximately 57 per cent (adults reactive to oleoresin)[38] Spain 65 per cent (adolescents and adults reactive to oleoresin)[45]

To secure meaningful figures on the rate of clinical sensitivity

one should use a realistic testing procedure that is one performed with fresh bruised leaves not extracts for reasons which will shortly become clear By this criterion no figures on a sizable population have been previously presented

The results of finger pressing bruised leaves to the forearms of adult males are shown in Table 25

The clinical incidence of sensitivity among whites was about 50 per cent which is in agreement with previous studies The per centage was significantly lower in pigmented skins Dr William Ep stein of our laboratory in a carefully controlled study has shown that the Negro is not nearly so susceptible to contact sensitization Kanof and Rostenberg[46] noted a somewhat lower incidence of poi son ivy sensitivity in adult Negroes Consistently Rostenberg and Kanof[47] found the Negro to be less readily sensitized to potent ex perimental contact allergens such as dinitrochlorobenzene and *p* nitrosodimethylaniline

PERSISTENCE OF THE SENSITIVITY

It is a prevalent opinion based on clinical impressions that con tact sensitization tends to last indefinitely Evidence is accumulating however that contact sensitization may diminish and even vanish even in the face of continued exposures Morgan[50] for example found that 43 per cent of nickel sensitive patients followed for 1 5 to 11 0 years lost their sensitivity This occurred independently of continued contact with the allergen Individuals differ greatly in this respect After experimentally sensitizing a group of 50 patients with dinitrochlorobenzene Wedroff and Dolgoff[1] found that more than half had become spontaneously desensitized within a year Pre sumably the loss of sensitivity would be most rapid in those whose original allergy was weak

It would be an agreeable feature of an otherwise entirely disagree able disorder if poison ivy sensitivity characteristically declined with time Of six newborn infants deliberately sensitized by Straus[5] one had lost his sensitivity when retested about 20 months later Shel mire[3] noted a definite loss of sensitivity in the aged In a Dallas con valescent home where the average age was about 70 years poison ivy sensitivity was rare in contrast to a 50 per cent sensitivity in young adults At a summer camp where poison ivy plants were rampant Zisserman[53] found a clinical incidence of dermatitis up to 50 per cent in the twelve to sixteen year age group but only 22 per cent for young adults above age twenty Of course data of this latter kind are merely presumptive in the absence of definite knowledge of ex

posure Kanof and Rostenberg[46] found a sensitivity rate of about 16 per cent in emotionally disturbed persons who had been incarcerated for an average of eleven years as compared with 25 per cent in a comparable unconfined group In my series the incidence of sensitivity to bruised poison ivy leaves in relation to age was as presented in Table 26

TABLE 26 SENSITIVITY TO BRUISED IVY LEAVES IN RELATION TO AGE

Age group	Number	% Sensitive to leaf
1-30	304	58
31-40	173	47
41-50	101	41
51-60	83	39
61-70	59	14

In the older age group the percentage of reactors was only one fourth that of young adults in the third decade The steady decline in sensitivity with age is probably not so much due to greatly diminished exposure as it is a general biologic tendency Furthermore among the aged high degrees of sensitivity are uncommon Clinical experience strongly suggests that the degree of sensitization is highest in childhood and thereafter tends to become less and less intense with or without continued exposure While some allowance should be made for the increased wariness of older persons as well as for diminished opportunity for exposure there is strong presumptive evidence that in quantity and intensity the peak is in youth as seems fitting To this rule as to all others there are qualifications High initial sensitivity does not decline rapidly in my clinical experience nonetheless I have encountered a score of immune adults who were severely troubled with poison ivy dermatitis in childhood

Both in this study and in the earlier survey of Keil *et al* [4] all poison ivy sensitive patients reacted to patch tests with 1 per cent PDC A positive patch test to 1 per cent PDC is not however a reliable guide to the existence of clinical sensitivity Indeed leaf sensitivity is usually absent unless the subject is sensitive to 1:10,000 PDC Through simultaneous quantitative patch testing with serial 10 fold dilutions of PDC in acetone (0.25 ml) and crushed leaves it was established that those who reacted to 1:10,000 PDC and beyond invariably got a dermatitis when exposed to leaves About one third reacting to 1:1,000 but not beyond this were clinically sensitive but none whose titer was only 1:100

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There were four children in each group The drug was administered by adding 1 cc of a 10 per cent alcoholic solution to a glass of water It may be mentioned that appreciable absorption is known to take place from the finding of antigenic substances in the urine and the elicitation of a variety of cutaneous lesions when even small amounts of this antigen are given by mouth to sensitive persons One week after the last dose each subject was exposed to a sensitizing stimulus consisting of 0 25 ml of 3 per cent PDC in acetone A month later quantitative challenge patch tests to 10 fold dilutions of PDC beginning with 1 100 were applied

Unfortunately no evidence of interference with the rate or degree of sensitization was obtained All of the control subjects and 11 of the treated ones became sensitized to varying degrees rarely to the extent of reacting beyond the 1 10 000 level All four groups showed comparable variations in the degree of sensitization

The failure in this preliminary study to demonstrate immunologic blocking in humans does not warrant final conclusions Factors to be investigated include total dosage spacing of doses absorption of antigen route of administration etc As yet the blocking effect in animals is completely inexplicable it may not even be a specific immunologic phenomenon but rather some pharmacologic property of dinitrochlorobenzene and arsenic which somehow interferes with the sensitization process As regards prevention of poison ivy sensitization there is as yet no evidence that this takes place spontaneously through earlier natural exposures to similar or related antigens Finally it should be noted that hyposensitization of already sensitized persons by administration of the antigen is a totally different phenomenon

CLINICOIMMUNOLOGY

Sensitization to poison ivy takes place through topical contact with the skin Straus[8] found that none of ten infants became sensitized when a potent alcoholic extract of the plant was applied to the back of the tongue Only one of ten infants was sensitized by subcutaneous injection Folklore tells us that Indian boys who sought immunity by chewing the leaves did not become sensitized One might surmise that this was done with great care not to touch the skin!

The reaction time the interval between contact and the appear

ance of the dermatitis is quite variable It is rarely less than six hours and sometimes is delayed 12 days In general it varies inversely with the degree of sensitivity being shortest in the exquisitely sensitive It is partly dependent on the quantity of antigen that is the intensity of the exposure As a general rule poison ivy dermatitis develops within 24 to 48 hours after contact In quantitative patch testing it tends to be least with the strongest concentrations and greatest with the weakest dilution This effect of concentration is not particularly obvious in highly sensitive persons nor indeed is it always obvious in the moderately sensitive Spain and Cooke[31] deny that concentration influences reaction time Hot weather shortens it There are innate individual differences For diagnostic or epidemiologic patch testing it is necessary to be cognizant of reactions delayed beyond four days In my experience such reactions are by no means rare At least a six day checkup is indicated Shelmire[1] noted delayed reactions ranging from 5 to 11 days

Perhaps the most variable feature of the dermatitis is its duration This needs great emphasis since treatment not nature is generally credited when the course is brief Healing time is partly dependent on the intensity of the dermatitis the greater the initial damage the longer the time for repair Other factors are operating however since the healing times of different persons with equivalent degrees of dermatitis vary from days to weeks

Quantitative patch testing is the most precise means of determining the degree or depth of sensitivity Attention is called to the fact that *a single patch test with a strong concentration may fail to distinguish between persons of different degrees of sensitivity* Estimating the degree of sensitivity from a single concentrated patch test is very much like using undiluted serum in the serologic test for syphilis and grading the reaction from 1+ to 4+ a practice now supplanted by quantitative tests Testing by titration with varying dosages is more accurate Some sample titration curves are shown in Fig 33 2

The skin of course is the preeminent shock organ in allergic contact dermatitis *To some extent it is happenstance that the skin has* come to be thought of as the exclusive site of the allergic reaction since it is generally the only part of the body sufficiently exposed to the allergen Clinically it is true that contact dermatitis is almost exclusively a skin disease biologically however the allergic tissues capable of reacting are more widespread possibly universal The mucous membranes participate to a lesser but definite extent To produce a reaction in the mouth the subject must be highly sensitive and the allergen concentration high Shelmire[3] produced in

flammation of the tongue and hard palate by putting 1 10 oleoresin on the tongue I suffered a severe almost incapacitating stomatitis by introducing 0 5 ml of 10 per cent PDC in sesame oil into my mouth spreading it around with the tongue Five subjects with mild or subclinical sensitivity were not harmed when 0 5 ml of 10 per cent PDC was put into their mouths This is an extremely high concentration Each of three highly sensitive persons to whom this was done developed a stomatitis of varying degrees There was no evidence of esophageal laryngeal or gastrointestinal distress When these same persons took 1 ml of 10 per cent PDC in capsules the

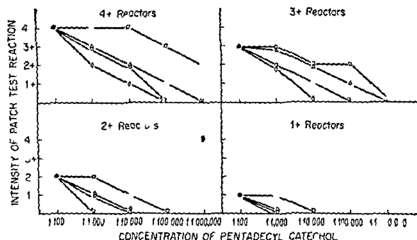


Fig 33 2 Variable pattern of dosage response curves based on quantitative patch testing Persons who react similarly to 1 100 PDC may in fact have quite dissimilar degrees of sensitivity as indicated by divergent titers In general however the titers tend to be proportionate to the intensity of the concentrated patch test reaction

only untoward reaction in two of them was pruritus ani Evidently the sensitivity is limited to or is detectable only in the mucous membranes adjacent to the skin

It would seem however that tissues other than the skin are capable of reacting provided that the antigen reaches them in sufficient concentration and the subject is sufficiently sensitive When 10 per cent concentrations of PDC are given intramuscularly the local and systemic effects in highly sensitive persons may be severe the muscles and subcutaneous tissues may become highly inflamed bearing the brunt of the attack but in addition there may be fever malaise grippe like syndromes hematologic changes and other responses

of a systemic nature[61] It is proposed that allergic contact dermatitis is biologically a state of generalized or systemic allergy Under the usual clinical circumstances the potentiality of other tissues to react does not become manifest Sidi and Dobkevitch Morril[6] noted a variety of constitutional reactions when patients with allergic contact dermatitis *were given allergens by injection or by mouth*

Flare ups of healed sites are well known in poison ivy dermatitis at the time of a fresh attack or after patch testing Shelmire[3] remarks that healed areas remain supersensitive for many months *reacting to concentrations of allergen that will not elsewhere produce* a dermatitis This has been verified in the current investigation with one important qualification namely that there is a variable period two to four weeks after healing in which the site is actually hyporeactive During this time the patch test may be negative or greatly lessened within the healed sites These altered reactivities are nonspecific in the sense of not having an immunologic basis parallel changes to primary irritants and nonrelated antigens can be demonstrated in previously dermatitic skin These generalizations hold for all forms of allergic contact dermatitis The occasional instance in which a positive patch test is limited to a previous site of healed dermatitis is not a demonstration of localized allergy as has been claimed but simply reflects the enhanced reactivity of previously damaged skin in a patient with a borderline sensitivity

The entire skin may become supersensitive when the dermatitis is widespread At such times patch tests formerly too dilute to provoke a reaction will do so This too is nonspecific in nature Other reactions (allergic or primary irritant) are elevated Dermatologists know full well the explosive quality of such skin and often postpone patch testing until the dermatitis has abated Less well known is the very antithesis of this namely a state of generalized hyporeactivity associated with a severe disseminated dermatitis I was several times deceived by this phenomenon which is somewhat analagous to the refractory state which ensues after sublethal anaphylactic shock I studied six persons with severe Rhus dermatitis who did not *react to 1 10 000 PDC All reacted to 1 100 PDC* At first I refused to believe that they were suffering from poison ivy dermatitis Within four to eight weeks however there was a gradual return to clinical levels of PDC sensitivity It would appear that some persons can become relatively refractory for a limited time after a severe antigenic shock This refractoriness is reminiscent of the anergy exhibited by gravely ill patients to antigens giving delayed reactions For want of a better expression the skin seems exhausted Some poison ivy patients venture the intelligence that they become

relatively immune for the remainder of the summer season after a severe spring attack The protection which they claim is susceptible of other interpretations but may be worthy of tentative belief in some instances In my experience refractoriness following a severe attack is not common

Shelmire[7] had previously come across the refractory state in a nurse to whom he had deliberately administered a large dose of oleoresin orally Her skin became fiery red and edematous but though her skin had been extremely sensitive previously the application of a bruised leaf provoked no reaction Other evidences of refractoriness were displayed by Shelmire s patients who developed pruritus dyshidrosis and widespread erythematous eruptions after a fairly large oral dose of oleoresin After these signs of intolerance disappeared the same or even double this dose was tolerated without mishap and the reactions to patch tests were depressed Shelmire does not make it clear whether he considers this a specific reduction in sensitivity in the immunologic sense I have verified the phenomena he describes The mechanism is unknown Temporary anergy to dinitrochlorobenzene has been observed in guinea pigs after multiple patch tests with this substance[63]

The usual manifestations of poison ivy dermatitis are well known and have been described in Chap 32 Contact Dermatitis They conform to the expected pattern of allergic contact dermatitis Rather characteristic but not unique is the tendency to form voluminous blisters

UNUSUAL MANIFESTATIONS

Because poison ivy dermatitis is by far the commonest of all allergic diseases in the United States and because it often exists in a severe widespread form an opportunity is provided to observe certain unusual phenomena which are generally not emphasized in connection with allergic contact dermatitis

Hematologic Changes Templeton *et al*[64] found that about one third of the patients requiring hospitalization for severe poison oak dermatitis had a leukocytosis ranging between 10 000 and 16 000 leukocytes per cu mm About an equal number showed eosinophilia generally ranging from 5 to 10 per cent The leukocytosis is not in itself a particular expression of allergy being a frequent concomitant of widespread dermatitis of any origin But the frequency of eosinophilia has been largely overlooked In this instance it is a specific hematologic response to the allergic stimulus or at least to the allergic reaction as it is in diverse allergic conditions In the present study complete blood counts were done on 14 patients with

severe poison ivy dermatitis. Eight of these had eosinophilia exceeding 5 per cent, the highest reaching 22 per cent. Leukocytosis, ranging from 10,000 to 18,000 leukocytes per cu. mm., was found in seven. Eosinophilia is a quite common development after hyposensitizing injections of PDC. Insufficiently appreciated is the fact of tissue eosinophilia at the site of allergic contact dermatitis, especially in the presence of hematologic eosinophilia. Three of six biopsies of intensely dermatitic skin showed local infiltration with eosinophiles. This is a distinguishing cytologic point between allergic and primary irritant contact dermatitis, which are often wrongly thought to be histologically identical. Pinkus[6] has commented on tissue eosinophilia in other types of allergic contact dermatitis.

Kidney Damage. Weeks after a severe poison ivy dermatitis, particularly if it is recurrent, signs of kidney damage may emerge. Rytand *et al*[66, 67] observed signs of renal tubular damage and the nephrotic syndrome in six of seven persons. The medical diagnoses included lipoid nephrosis, glomerulonephritis and lower nephron nephrosis. It is highly significant that only one of these cases received phylactic injections of poison ivy antigen during the acute dermatitis. Shaffer and Burgoon's[68] report of two cases of glomerulonephritis, one fatal, after four injections of poison ivy antigen during the dermatitis has justifiably caused considerable alarm. Their conclusion that the injections (which actually contained only minute amounts of allergen) evoked an allergic response in the kidney is open to considerable doubt. While the possibility of allergic renal disease cannot be ruled out, the evidence is not at all convincing. A more probable explanation, adequately considered by Rytand, is that the glomerulonephritis is a consequence of secondary bacterial infection of the widespread dermatitis. The latent period of several weeks or more strongly suggests this. Pyoderma has been implicated as a preceding causative event in glomerulonephritis.

McNair's[1] finding of proteinuria in 50 per cent of poison ivy cases was not confirmed by Templeton *et al*.[64] In the present study albuminuria was not present in any of the twenty-one severe cases whose urine was examined at the height of the dermatitis. Nor did albuminuria or other urinary abnormalities occur significantly in subjects receiving hyposensitizing injections of PDC, even with massive doses.

Wheal Reactions. Bouts of urticaria were seen in two patients during severe attacks of untreated Rhus dermatitis. Of many questioned only a few could recall such a happening. When the dose is too large or the patient extremely sensitive, urticaria is a quite com

mon side reaction during Rhus hyposensitization therefore it is known that Rhus allergens have at least the potentiality of evoking urticaria However urticaria and contact dermatitis belong to different allergic categories the immediate and delayed types respectively these are immunologically distinct

The presence of circulating serum antibodies in the former is a valid distinguishing feature Also the rapid emergence and dominance of the vascular effect (edema) are quite characteristic It is coming to be better understood that immediate and delayed type allergies to the same allergen may coexist While it is clinically helpful to classify allergic disorders into one or the other type according *to which manifestations are dominant such a classification is inconsistent* with biologic fact Chase s[69, 70] researches have greatly illuminated this subject He states that every immunologic stimulus gives rise in some measure to both immediate and delayed type components one usually predominates Focusing upon allergic contact dermatitis in particular Landsteiner[71] and Landsteiner and Chase showed many years ago that animals rendered contact sensitive to picryl chloride died in anaphylactic shock when intra*venously injected with picryl chloride protein conjugates It should* be noted that a special protein conjugate of the haptene not the simple chemical is generally needed to disclose the immediate type allergy Eisen[73] has found that some contact allergens readily produce circulating antibodies along with contact sensitization while others induce only contact allergy The immediate type allergy which may coexist in the individual with allergic contact dermatitis generally remains hidden a potentiality which does not ordinarily *reach clinical expression It we think of the antibody factory* as a two pronged system immediate antibody synthesis to contact allergens is the shorter inconspicuous prong Horsfall[74] had a patient with extreme contact sensitivity to formalin who reacted immediately with wheals upon intracutaneous testing with formalized protein conjugates this was followed by the typical delayed response In guinea pigs sensitized by contact to certain anhydrides (citraconic phthalic etc) Jacobs [5] was able to produce wheals even *without prior conjugation simply by scratch testing with the pure* chemicals

With this background we may now examine immediate type allergy in Rhus dermatitis Dermatitis not urticaria is the invariable local reaction at sites of contact The requirement for the development of wheals is the hematogenous distribution of a sufficient quantity of antigen (presumably a catechol protein conjugate) to the skin of a highly sensitized person Because of the skin s impermeability

external contact rarely enables enough antigen to reach the blood stream and therefore it is particularly by ingestion or injection of larger quantities of allergen during hyposensitization that urticaria is evoked As a rule the hives do not begin to appear before 12 to 24 hours and so the reaction is not immediate in time but only morphologically The latent period possibly represents the time required for formation and distribution of the proper conjugate When the contact sensitization is weak even a fairly large intramuscular injection of PDC (100 mg) fails to evoke wheals presumably because the titer of circulating antibodies is too low Contrariwise this same dose will produce urticaria in almost every highly sensitized person

The greater the contact sensitization the more likely it is that the weaker immediate type allergy may reach the clinical level of detection It is only in the exquisitely sensitive that generalized hives may develop from simple external contact with the plants This is rare It should be firmly understood that urticaria is not a manifestation of allergic contact dermatitis but merely an associated phenomenon The severest manifestation of the immediate type allergy which may be associated with the state of contact sensitization anaphylaxis has fortunately not been witnessed in humans The probability of such an event is remote even when the haptene is injected or ingested

In his beautiful animal studies Chase[69] has made an acute observation which has been generally overlooked He has noted the blending of the urticarial and eczematous reactions in the lesions of allergic contact dermatitis This is essentially a clinical demonstration of the coexistence of the immediate and delayed type allergies *at the same site The typical eczematous response is of course dominant* at sites of contact but surrounding it and often subtending it there may be considerable urticarial swelling Students of human allergic contact dermatitis have undoubtedly encountered this swelling reaction many times in highly sensitive persons but by considering it secondary to the severe eczematous reaction have probably missed its true significance In addition the very intensity of the eczematous response masks the giant hive which subtends it I have frequently seen such blended lesions in cases of severe poison ivy dermatitis The explanation is attractive that such patients have circulating antibodies in sufficient titer to elicit the urticarial response concomitantly with the eczematous lesion

In a meticulous study of the Arthus phenomenon which is an immediate type allergy Gell[76] has found in the same lesion histologic changes which are characteristic of the immediate and the

delayed response For years Kallos[77] has been insisting that there is no principal histologic difference between the lesions of immediate and delayed type allergies and that it is merely one of degree and duration Histologic studies of allergic contact dermatitis in our laboratory lead us to concur in this concept

Id Reactions A variety of erythematous macular and papular rashes occurs during hyposensitization with Rhus allergens Such ids may develop spontaneously during severe attacks of Rhus dermatitis in the highly sensitive patient Such lesions may result from hematogenous distribution of absorbed allergen as well as at sites of contact

Dyshidrosis The palms are usually exempted in poison ivy dermatitis because of the impenetrability of the thick stratum corneum However an occasional highly sensitive patient presents the picture of dyshidrosis This reaction may be straightforward contact dermatitis or an allergic id due to hematogenously distributed antigen especially during hyposensitization or occasionally may result from absorbed antigen after external contact in the highly sensitive

Pigmentary Changes Leukoderma with hyperpigmentation is occasionally a sequela of Rhus dermatitis[78]

EXTERNAL OR TOPICAL PROPHYLAXIS

A number of prophylactic measures are advocated by persons who are particularly concerned with the prevention of poison ivy dermatitis viz outdoorsmen mothers and camp directors These practices which are thought to prevent or moderate the ensuing dermatitis include (1) removal by washing or solvents (2) barrier creams and (3) detoxicants (oxidizing and complexing agents which chemically inactivate the antigen)

1 Removal by Washing Washing with strong laundry soap after an exposure has enjoyed great popularity When examined critically however the benefits become dubious Shelmire[3] was unable to alter the dermatitis significantly by soap and water washing for five minutes immediately after rubbing leaves on highly sensitive persons! There was some moderation in mildly sensitive persons when the washing was done within 5 to 10 minutes Typical of the stark conflicts which abound in poison ivy studies is Pfaff s[79] claim that soap and water washing will prevent the dermatitis if done within a few hours of exposure and will abort an attack in the vast majority even after vesicles have appeared! To explore this question further I applied bruised leaves to the forearms and washed vigorously (with Ivory soap) for 2 minutes at the following intervals after

exposure 1 minute 5 minutes 10 minutes 30 minutes 60 minutes Two groups of four adult subjects each were employed the first group were highly sensitive giving patch test reactions to 1 1 000 000 PDC The second were borderline cases of clinical sensitivity reacting to 1 10 000 but not 1 100 000 PDC

The results are presented in Table 27

TABLE 27 EFFECT OF WASHING ON DERMATITIS

	Subjects	Control	Minutes after exposure 1	5	10	30	60
High sensitivity	1	++++	++	++++	++++	++++	++++
	2	++++	+	+++	++++	++++	++++
	3	++++	+	++	++++	++++	++++
	4	++++	+++	++++	++++	++++	++++
Borderline sensitivity	1	+	0	0	0	0	+
	2	+	0	0	0	+	+
	3	+	0	+	0	+	+
	4	+	0	0	0	0	+

In the highly sensitive washing which is delayed until 5 minutes after exposure will do very little good In the mildly sensitive washing within 30 minutes may prevent the dermatitis in some but not after 1 hour While these results are somewhat more favorable than Shelmire s one must agree with him that washing has very little practical merit under average field conditions Essentially the same results were obtained with medicinal soft soap U S P (semisolid green soap) and when a solvent consisting of equal parts of acetone and ether was substituted for ordinary soap From these studies it seems evident that penetration and/or fixation of the antigen in the skin is extremely rapid

2 **Barrier Creams** Tests were carried out with representatives of the two main types (1) against water (silicone cream) * and (2) against oils † Four highly sensitive subjects were used White petrolatum served as the control The ointments were applied to the forearms and crushed leaves pressed down 30 and 60 minutes later The silicone cream proved valueless After 30 but not 60 minutes there was a slight to moderate suppression of the dermatitis

* The silicone cream was Pro-Derma (Westwood Pharmacal Corp) contains approximately 50% silicone

† The formula for the oil type barrier was hydrous wool fat (Lanolin) 25% castor oil 25% ceresin wax 64C 5% polyoxyethylene sorbitan mono stearate (Tween 61) 5% white petrolatum 40%

with the oil barrier cream but the results were not superior to plain petrolatum It is concluded that barrier creams offer no practical degree of protection against poison ivy dermatitis

3 Detoxicants Chemical inactivation of the allergen is a logical possibility in topical prophylaxis The many efforts along these lines are attractive because they have a rational chemical basis Offhand it would seem that the task of finding a chemical inactivator should not be difficult the practical handicaps however are really very great when one considers that the antigen penetrates quickly and soon becomes inaccessible The detoxicant must therefore intercept and destroy the antigen before any of it gets into the skin Furthermore the test tube conditions of inactivation are a far cry from what happens on the skin s surface

Detoxicants are mainly of two kinds (1) oxidants (potassium permanganate hydrogen peroxide sodium perborate iodine etc) and (2) complexing or chelating agents which form chemical combinations Many of these are salts of heavy metals (iron zirconium silver barium manganese etc) Often the inactivation is slow and would probably not take place with sufficient speed on the skin s surface Another limitation emphasized by Gisvold[80] is that many agents such as ferric chloride which precipitate the antigen in vitro do not thereby inactivate it

Howell[33] was unable to prevent the dermatitis with strong ferric chloride or sodium perborate solutions The application of 10 per cent (!) potassium permanganate within 5 to 10 minutes did have a moderating effect in moderately sensitive subjects Shelmire[31] disproved the claim of Schwartz *et al*[81] that sodium perborate detoxified the antigen in vitro and that 10 per cent ointments could prevent the dermatitis While it may be true that the enzyme tyrosinase catalyzes the oxidation of Rhus antigens in vitro its capacity to prevent a dermatitis when applied a few hours after exposure which Sizer and Prokesch[3] aver must be doubted Recently enthusiastic claims have been made for a modern complexing agent zirconium * generally prescribed in the form of hydrous zirconium oxide It is said to prevent the dermatitis even when applied an hour after exposure After noting that synthetic phenol formaldehyde resins (Amberlite) could remove Rhus antigens from solution Thurmon *et al*[83] found them superior to zirconium an anticholinergic cream * hydrocortisone and a control (in that order of effectiveness) when applied 2 to 9 hours after contaminating the skin with oleoresin It is unlikely that this will be confirmed

I have conducted innumerable tests with a galaxy of materials

* Trantal cream (Schering)

purported to abort poison ivy dermatitis In general the procedure consisted of applying the prophylactic agent 1 hour before and in another site 1 hour after a standard leaf exposure A third site received no treatment (control) The subjects were all adult male prisoners of high degrees of susceptibility My original mild optimism has degenerated into lack of confidence that topical prophylaxis can be made practical by any of the methods so far conceived Rather than list the thirty four preparations that were tried over a two year period I need only say that they were representative of the kinds usually recommended None had any effect It is worth pointing out that the allergic process is probably well under way within an hour or two perhaps irreversibly so even if it were possible to inactivate excess surface allergen

HYPOSENSITIZATION *

Specific hyposensitization by the administration of Rhus antigens is attainable to a limited but definite degree In a controlled study of more than 2 000 subjects hyposensitization was found to occur either by oral or intramuscular administration of the Rhus allergens With oleoresin maximum hyposensitization was obtained with 2 000 to 2 500 mg intramuscularly and with 3 500 to 4 000 mg orally This required 5 to 9 months of treatment and approximately twenty two injections of the oleoresin yet claims have been made for commercial products containing only 5 to 20 mg per dose with only a few doses given More astounding some of the preparations employed were found to be completely inert A control study in which injections of sesame oil alone were given to eighteen highly sensitive volunteers gave satisfactory results (to the patient) in sixteen instances while the post treatment patch tests showed no decline

The synthetic allergen (PDC) also produced hyposensitization but this required a higher dosage than the oleoresin In no instance however was there complete hyposensitization in persons with high sensitivity

In a limited study of an alum precipitated pyridine extract of poison ivy (Aqua Ivy) there was no confirmation of the findings of Passenger [101] and Gaillard [103] who claimed extraordinary protection with this type of antigen Since patch testing with the pyridine extract is always negative it is assumed (but no evidence has been presented) that the inert allergen is converted into active allergen

* This is the editors summary of a special study on hyposensitization by the author to which the reader is referred [104]

in the tissues following injection It is highly improbable that a substance incapable of producing a dermatitis can be useful for hyposensitization

A recent report by Langs Fuchs and Strauss[107] in a limited but controlled study claimed that the positive patch test could be de creased or made to disappear with Aqua Ivy tablets I could not con firm this

Hyposensitization occurs in a definite pattern as revealed by quan titative patch tests The reaction to the highest dilution declines first and only the terminal portion of the dosage response curve is notably affected A given fraction of the original sensitivity may be abolished but no more regardless of dosage or sensitivity of the patient

By repeatedly assaulting the skin with dermatitis producing patch tests over a period of many months complete clinical desensitiza tion to poison ivy leaves can be achieved This is a form of harden ing On the other hand complete desensitization of the *highly sensitive* subject by oral or intramuscular injection is impossible

A variety of systemic and mucocutaneous side reactions may de velop in the course of hyposensitization accompanied by charac teristic changes in the blood (eosinophilia) The severity and fre quency of these are proportional to the dosage and the sensitivity

When achieved hyposensitization is only temporary It begins to wane in a few weeks and the original sensitivity is gradually re gained within 6 to 10 months occasionally longer

In view of the limits of hyposensitization its general use is ques tionable It is indicated however for severely sensitive persons who cannot avoid poison ivy dermatitis Although complete hyposensi tization may not be achievable prophylaxis may result in dermatitis briefer in duration with less dissemination and a milder form

THERAPY

Therapy may be either (1) topical or (2) systemic

1 **Topical Therapy** The long standing effort to find an effective topical medication for acute poison ivy dermatitis is not one of the proud chapters in the history of medicine Furor therapeuticus is much in evidence in the literature McNair[1] treats the subject ex tensively—and rather uncritically Quantitatively the number of treatments which have at one time or another been admired is prodigious Qualitatively they range from the preposterous to the fantastic The stream of new therapies continues to flow briskly A brief listing of some of the more interesting agents which have been

thought beneficial clearly reveals the profound emotional effects of therapeutic desperation morphine (topically!) bromine kerosene gunpowder (the symbolism here is beautiful) iodine aqua regia (!) buttermilk cream and marshmallows (!) and innumerable botanicals such as snakeroot coffee gelsemium hellebore ipecac lobelia mustard opium strychnine (!) veratrum etc etc Throughout there is a remarkable disregard for a simple biological fact namely that poison ivy dermatitis is a self resolving process Perhaps it is inevitable that physicians insist on taking credit for what is accomplished by nature There is a notable want of controlled experimental study in substantiating therapeutic claims Variables which make objective evaluation difficult in office practice or in field trials include intensity of exposure (amount of antigen deposited on skin) degree of sensitivity and natural course without treatment These limitations can be largely overcome by using *the same subjects* giving standard exposures (preferably with the leaf) and including two controls (1) untreated dermatitis and (2) treatment with the unmedicated vehicle

To make a long and frustrating story short I have not found in a long series of tests using a panel of 5 highly sensitive subjects a single topical agent or prescription among more than 30 tried which unmistakably influenced the course of acute poison ivy dermatitis when compared with standard bland dermatologic treatment (simple compresses and nonmedicated shake lotions or creams) The agents were applied t i d beginning 12 hours after the leaf exposure

A word is in order concerning topical corticosteroids since these conceivably could suppress the inflammatory response set off by the allergic reaction Topical hydrocortisone and its derivatives tend to be indiscriminately used for all kinds of dermatitis Kalz and his coworkers[84] used 1 to 2 5 per cent hydrocortisone ointments and state that the effect was striking and most satisfactory in the large majority of cases of contact dermatitis Topical fludrocortisone acetate has been thought to be beneficial in acute dermatitis[85] In carefully controlled studies with a variety of contact allergens given at threshold concentrations so as to provoke a borderline dermatitis we have been unable to demonstrate any moderating effect of topical hydrocortisone regardless of the frequency of applications even when the treatment was begun within 10 minutes after application of the allergen The agents used included prednisolone hydrocortisone (free alcohol and acetate) fludrocortisone and several soluble salts of hydrocortisone derivatives This topical ineffectiveness may be contrasted with the marked suppressive effect on allergic contact

dermatitis obtained by prior injection at the test site with 1 mg of hydrocortisone and 0.1 mg fludrocortisone Evidently topical application to an acute dermatitis is futile because of an insufficient tissue concentration probably owing to inadequate penetration and too rapid diffusion

The lack of a specific therapy for poison ivy dermatitis does not mean that topical dermatologic measures should be abandoned The treatment of Rhus dermatitis is the treatment of contact dermatitis in general the problem is not a special one and calls for the non specific time honored methods of managing eczematous eruptions secundum artem These are directed at supporting the self righting mechanisms of the skin and promoting the hygienic conditions which favor healing (baths compresses bland lotions and creams) The treatment of the pruritus is the treatment of the dermatitis which causes it A highly effective topical antipruritic agent is not yet at hand

2 **Systemic Therapy** Corticosteroids and corticotropin have revolutionized the treatment of allergic contact dermatitis The great majority of cases will be benefited by the equivalent of 100 mg of cortisone or 10 units of corticotropin daily It is wise to begin with two to three times these dosages for the first day or two An occasional highly sensitive individual will not be helped by any dose

In controlled studies with quantitative patch testing using PDC the following antihistaminic agents exerted no effect on the dermatitis (the drugs were given one day before the allergenic stimulus and were continued daily during the active dermatitic stages) (1) diphenhydramine hydrochloride (Benadryl Hydrochloride) 100 mg daily (2) tripelennamine (Pyribenzamine) 200 mg daily (3) chlorpheniramine maleate (Chlor Trimeton Maleate) 16 mg daily

Exclusive of corticosteroids no oral or parenteral drug has been clearly demonstrated to beneficially influence the course of allergic contact dermatitis

Antigen Therapy of Acute Poison Ivy Dermatitis About 1915 two Philadelphia physicians began to treat fire with fire and recommended injections of Rhus oleoresin to control the acute dermatitis[86-88] It will be instructive to dwell upon the extraordinary credulousness of physicians for this unproved recommendation It should be noted that the subject here is phylaxis not prophylaxis In introducing the toxin treatment of acute poison ivy dermatitis Strickler[88] presents the following extraordinary statement The almost magic rapidity with which the amelioration of the itching associated with this affection occurs the rapid subsidence of the lesions the uniformity with which good results are obtained and the

avoidance of uncomfortable moist applications recommended under the old method of treatment suggest that this method marks a distinct advance in the curability of dermatitis venenata due to *Rhus toxicodendron* Two to five injections of an alcoholic extract were advocated usually two sufficed With the mounting enthusiasm characteristic of uncontrolled observation this same author had occasion to note later that improvement occurs in the vast majority within 24 hours and sometimes even in 2 hours! Only 5 per cent of 356 cases failed to show this splendid result At a dermatologic symposium in 1925 [89] Schamberg remarks that progression of the dermatitis immediately ceases if antigen is used Eminent physicians of the day forthwith confirmed these wonderful benefits at the same symposium There followed a rash of papers extolling the treatment [90-9] The potency of the oleoresin extracts was of course totally unknown Duncan s [98] antigen treatment of the same era was even simpler The afflicted person had only to chew the leaves making sure to use the very same leaves that had caused the dermatitis and not others! To forestall any question of credit he is careful to point out that his method is autotherapy not homeopathy Skeptics of the toxin treatment were not much in evidence however, it was happily another Philadelphia physician Corson [99] who first found the toxin therapy not only worthless but also dangerous recording a case of generalized vesicular dermatitis provoked by the injections Later in 1938 another minority voice was Sompayrac [100] who did a controlled study and found the method valueless Templeton [101] devoted an essay to untoward reactions mostly urticaria about which the earlier enthusiasts were strangely silent Goldman [10] observed distressing reactions in four patients including local swelling at the injection site urticaria vesicular eruptions and generalized pruritus Howell [103] tried the treatment without success in 1947 noting untoward eruptions and even prolongation of the original dermatitis Wondering why his predecessors had not got into more trouble he supplied an interesting and whimsical answer The commercial extracts were so weak and degraded that he could find only three of eight brands with sufficient traces of antigen to incite a dermatitis by patch test in a highly sensitive subject! Perhaps some consolation is to be found in the fact that if the extracts were for the most part impotent they were at least so weak as to be almost completely harmless One is confronted with the quixotic fact that many physicians achieved remarkable results with an extract biologically equivalent to water!

The following study extends Howell s observations A series of subjects of varying sensitivity were patch tested with four commer

cial brands of Rhus oleoresin In general these preparations are made up to contain about 0 1 per cent solids (oleoresin) sometimes a little more The titer of each subject had been previously determined by serial patch testing with PDC The results were as presented in Table 28

TABLE 28 RESULTS OF TESTING WITH COMMERCIAL BRANDS OF RHUS OLEORESIN

PDC sensitivity titer	No subjects	Reactors to brand #1	#2	#3	#4
1 100	3	0	0	0	0
1 1 000	2	0	0	0	0
1 10 000	3	0	1	0	0
1 100 000	2	0	2	2	0
1 1 000 000	1	0	1	1	1

Of the four brands one was totally impotent and conversely only one was sufficiently active to give a reaction at the level of clinical sensitivity 1 10 000 The reason why it is usually safe to use such preparations in the treatment of the acute dermatitis is obvious The original concentration is fairly low and with time there is a tendency toward deterioration however I have had some batches of 0 1 per cent oleoresin in sesame oil which were fairly stable over a two year period and others which deteriorated The variability and instability of crude extracts are a great disadvantage In fairness it should be noted that the manufacturers of such extracts generally do *not* recommend their use for treatment of the acute dermatitis but rather for prophylaxis

To gain more information on the hazards of phylactic treatment I deliberately administered 0 2 cc of 10 per cent PDC in sesame oil intramuscularly to 11 patients with acute poison ivy dermatitis The injection of this quantity (20 mg) into two highly sensitive patients with a generalized dermatitis resulted in their hospitalization with the following findings temperature to 104 F leukocytosis (up to 18 000 leukocytes per cu mm) eosinophilia (11 per cent and 18 per cent respectively) headache malaise intense coughing in one case and meningismus in one case The urinalyses were normal as were BUN and chest x rays There were intensification of the dermatitis generalized pruritus generalized erythematous exanthem and in one generalized hives A severe cellulitis occupied the site of injection with soreness great swelling and pain Both responded

promptly to intravenous corticotropin 40 units daily supplemented by 100 units of cortisone daily by mouth

Five other persons developed adverse reactions as follows (no blood studies or urinalyses done)

urticaria	3
dyshidrosis	1
fever	4
exanthem	2
pruritus	4
cellulitis of injection site	5
exacerbation of dermatitis	2
malaise	3
grippe like symptoms	2

Neither these five nor the preceding two developed a spontaneous vesicular eruption (excepting one instance of dyshidrosis) All responded satisfactorily to corticosteroids The remaining four cases remained free of important side reactions save for local pain and swelling at the injection site in two cases Those who escaped were not always the least sensitive It may be concluded that there is a very high likelihood of untoward reactions not grave but distressing when a significant quantity of antigen is given during the acute attack In highly sensitive persons adverse reactions are almost a certainty if the equivalent of 20 mg of PDC is given

The administration of an allergen which is the cause of an already existent dermatitis is senseless and contraindicated This principle is so paramount in dermatology that it is almost a universal rule to postpone even patch testing during an acute allergic contact dermatitis To bombard sensitive tissue via the hematogenous route can only add to the patient s woes

It is disappointing to note that current authors can find some merit in antigen therapy [104, 10] My experience with hundreds of poison ivy patients indicates that the therapeutic intramuscular injection of oleoresins is still very much in vogue This practice is to be condemned in the strongest terms

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34 | *Marion B Sulzberger*

ADRENAL CORTICAL STEROIDS AND ALLERGIC DERMATOSES

The record of modern medical history shows clearly that fundamental physiologic and medical knowledge has often been acquired through study of the skin its reactions and diseases Nowhere is this truth more apparent than in the sphere of endocrinology and that of the adrenal hormones—in particular in their relations to allergic dermatoses

The reasons for this may be seen in the fact that both the adrenal glands and the skin are organs most intimately concerned with the adaptation of man to his environment and that the immunologic and allergic changes are primarily and predominantly reactions of adaptation Often it is the adrenals which send out hormones to stimulate and regulate the adaptive and protective changes while other organs such as the skin respond by producing the required local adaptive reactions

Among the nonimmunologic adaptive and protective reactions of the skin are its production of pigment horny substance sweat and sebum its pilomotor reflexes its vasodilatations and constrictions its arteriovenous shunts and its sensory warnings of touch heat cold pain and itching All these are parts of the human skin s main function adapting the individual to and protecting the individual from the chemical and physical living and inanimate onslaughts of his environment Moreover it must not be forgotten that the skin s allergic reactions and lesions are also protective and adaptive mechanisms although often so miscarried as to do more harm than good

(at least locally and temporarily in the sites where they take place) In the common allergic skin diseases the skin is working to throw out wash off and carry away *potential injurious agents* by blistering weeping and accelerated scaling (contact type eczematous dermatitis) or acting to dilute them and carry them away by edema (urticaria angioneurotic edema wheals from stinging nettles and insect bites etc) or proceeding to wall off destroy and eliminate infecting microorganisms by cellular infiltration by phagocytosis by local crusting and necrosis by fibroblastic proliferation etc (cutaneous reactions in allergies of infection tuberculosis syphilis leprosy fungous infections etc)

Since many of the described dermatologic immunologic protective devices are directly or indirectly stimulated and regulated by the adrenal hormones it is not surprising that there are close relationships between adrenal function and allergic skin reactions and skin diseases

On the basis of such purely theoretic considerations it was predictable that the administration of the adrenocortical steroids would exert profound influences on both skin functions and allergic skin lesions I believe that recent dermatologic experience with adrenal steroids has amply demonstrated the accuracy of this prediction for it appears to me that no recent advance in medicine has had a greater impact on the understanding and management of both allergic and nonallergic skin diseases than has the introduction of ACTH cortisone hydrocortisone and their derivatives

Several other facts are the almost inevitable consequences of the basic theoretic considerations which have just been sketched briefly Thus it was to be expected that the effects of the steroids would be *nonspecific* i e they would act on the erythema exudation edema infiltration fibroblastic repair pain and itching of the skin the resultant phenomena of pathologic happenings almost regardless of their widely differing intermediate mechanisms or original causes It was therefore also to be expected that the hormones would not be in and of themselves curative but would suppress the disease manifestations i e would be morbidistatic Moreover it was almost inevitable that the administration of the hormones would be beneficial when the skin changes which they inhibited were actually producing more harm than good (i e *excessive* itching blistering scaling erythema) and conversely would be harmful when administered in cases in which the skin lesions were in themselves highly beneficial (because they serve to wall off confine or cast out the damaging agents as in tuberculosis certain pyodermas and other localized skin infections) It also was always apparent that when the

body s other maneuvers and devices were excessively increased by the administration of the hormones grave harmful effects might be produced for example hypersecretion of the gastric mucosa and consequent gastrointestinal ulcerations persistent elevation of blood sugar and consequent diabetes too much accumulation of fluid in the tissues and consequent weight gain cardiac damage etc excessive fears agitation and sleeplessness and consequent psychoses and other such hyperphysiologic effects

The very first practical deduction to be made from these fundamental concepts is that just as before the advent of corticosteroids in each case every modern means must be used to establish the diagnosis of the skin disease as accurately as possible and in each patient with an allergic (or other) dermatosis the causes must be sought and if possible reduced or eliminated as assiduously and thoroughly as ever In this connection it is important to recall the studies showing that administration of cortical hormones in the usual therapeutic doses does *not* regularly or significantly alter the responses to the usual forms of skin testing *when standard concentrations of allergens* are employed [1] These results indicate that skin tests can and should be performed even in patients under treatment with the hormones Failure to use every possible means to discover causal allergens and willingness to be content with merely giving the hormones are just as medically unsound as it would be to confine oneself to administering morphine for a gluteal pain without examining the patient and discovering and removing the tack on which he is sitting

Of course allergic skin disease should not as a rule be treated with the *steroid hormones alone* There is not only no general contraindication to the addition of appropriate local therapy but on the contrary this should be added whenever indicated (including topical medicaments radiation with roentgen and grenz rays etc) Indeed it is my own opinion that the most substantial benefits which these hormones bring often lie in their ability to complement aid and augment the effectiveness of properly selected topical therapy A blistering weeping hot and swollen oozing or scaly eruption will commonly tolerate no form of lotions ointments or pastes no tars or quinolines no rays or other effective topical agents The judicious systemic administration of cortical steroids will frequently in a matter of hours transform the acutely erupting angry and universally intolerant skin surface which would throw off and wash off all external remedies *into a smooth and docile area which will not only* tolerate and retain but derive great benefits from the appropriate dermatologic topical medicaments which may of course include

topical hydrocortisone when indicated But it is not only external medication which should be used in conjunction with steroid therapy the physician must also utilize to their fullest the concomitant beneficial effects of indicated internal and systemic medication (including antibiotics and other anti infectious agents antihistamines antipruritics tranquilizers sedatives etc)

Moreover the patient receiving cortical steroids must be kept under constant medical surveillance and generally medicated as needed Thus the existing or potential undesirable effects of the hormones should be counteracted whenever necessary by sodium chloride–poor diets diuretics potassium additions anabolic agents like testosterone and high protein diets diets to control or prevent diabetes insulin sedatives tranquilizers electroshock etc

It is not usual and perhaps not usually desirable to discuss the ill effects of a medication first But in the case of systemic administration of cortisone and derivatives the potential for damage is so great and so omnipresent that I believe it should be stressed as early and as vigorously as possible It is my opinion that the following rules should be engraved on every physician s mind if not on his office walls and on his prescription pad

1 Never give these hormones unnecessarily that is when the disease is not serious and is not a cause of very great suffering serious incapacity or a threat to life

2 Never give these hormones one day longer than needed or in a dosage higher than needed to establish satisfactory control over a threatening or intolerable situation

3 Never rely on them to the exclusion of other indicated diagnostic and therapeutic measures Whenever possible combine them with the best other measures available

4 Never give them to a patient in whom other less potentially harmful measures may prove equally effective

5 Never give them without first taking a history and giving a thorough sharply focused examination Never start them without first taking into consideration any contraindications which may exist (gastrointestinal ulcers active or formerly active tuberculosis diabetes psychoses hypertension cardiovascular disease etc)

6 Never fail to take the necessary measures to counteract or to reduce the risk of undesirable effects

7 Never fail to see that the patients are examined regularly to discover any incipient ill effects and to institute appropriate measures (I examine patients once weekly for gain in weight changes in psyche blood pressure fluctuations urinary sugar levels and general physical and mental findings when they are on a daily oral

dose of 75 mg or more of cortisine or equivalent and once every two to four weeks with doses of less than 75 mg daily)

8 Except for research purposes give the hormones only when the skin disease has been classified as one known to be generally responsive to this form of therapy

9 When the dose is high (over 75 mg of cortisone daily) and the period of uninterrupted administration has been prolonged (over three to four weeks) do not stop medication abruptly unless this step is absolutely essential Reduce the dose gradually over a period of weeks to months

10 When any emergency is expected or arises (surgical intervention intercurrent infection other stress) raise the dose substantially above the maintenance level (for example from 75 to 150 mg daily) for a short period before during and after the stressful situation (This should be done even in patients to whom steroid hormones have recently been administered but who have not received any for several weeks before the stressful situation)

By observing these rules and other common medical and common sense practices the physician can help many patients with formerly fatal dermatoses to stay alive (e g pemphigus acute disseminated lupus erythematosus severe drug eruptions exfoliating erythrodermas) Moreover he can tide patients with many acute dermatoses over the severely distressing and incapacitating periods of their skin eruptions (e g severe acute contact dermatitis such as sometimes arises from poison ivy dyes cosmetics external medicaments etc severe acute urticaria and angioneurotic edema severe erythema multiforme bullosum and Stevens Johnson syndrome severe allergic purpuras exfoliative erythrodermas etc from drugs and other causes severe acute pruritus from various causes)

The allergic and other benign dermatoses in which the steroid hormones can be of significant morbidistatic value in severe or intractable cases may be classified as shown in Table 29

In the severe chronic dermatoses such as otherwise intractable atopic dermatitis the maintenance doses can often be given in very gradually descending amounts and quite safely over long periods of time Thus there are now quite a few patients with chronic previously intractable skin diseases such as extensive incapacitating exfoliating erythroderma or severe chronic atopic dermatitis who originally needed 200 to 300 mg or more of cortisone (or equivalent) per day in order to relieve their distressing itching and skin lesions and who now after very gradual reduction of dose through several years are maintained in a completely satisfactory state by doses of 10 to 25 mg daily There are even some who at the moment require

no cortisone at all! It is gratifying therefore to record that a great degree of long lasting relief can be brought to a fair proportion of sufferers from certain chronic skin diseases diseases which as a colleague once expressed it to me do not end life but completely ruin it

So it seems that the administration of cortisone and related steroids far from interfering with the healing powers of tincture of time and far from inhibiting natural acquisition of resistance to these serious skin diseases either aids in the production of adequate resistance or at least does not interfere with nature s curative forces[3]

TABLE 29 BENIGN DERMATOSES IN WHICH ACTH AND/OR STEROIDS ARE VALUABLE AS ADJUVANTS IN SEVERE OR INTRACTABLE CASES

Dermatoses ordinarily of self limited course in which the short term administration of the hormones can act as a morbidistatic agent
- *Eczematous contact type dermatitis*
- Acute urticaria and angioneurotic edema
- Certain drug eruptions (purpuric urticarial exfoliative etc)
- *Multiforme erythemas*

Ordinarily nonfatal persistent chronic or recurrent dermatoses in which the prolonged administration of the hormones can act as a morbidistatic agent
- Atopic dermatitis (including infantile eczema)
- Exfoliative erythrodermas
- Nummular eczema
- Eczematous eruptions of the hands
- Distinctive exudative discoid and lichenoid chronic dermatosis (Sulzberger and Garbe)
- Chronic urticaria
- Seborrheic dermatitis (particularly in intertriginous areas)
- Psoriasis of the erythrodermic pustular and arthropathic varieties particularly in intertriginous areas

It would be misleading however to give even the momentary impression that *all* patients with chronic incapacitating skin diseases can now be relieved and rehabilitated There are unfortunately still many in whom the necessary doses of hormones are contraindicated or must be stopped because they produce uncontrollable and prohibitive undesirable effects So I must repeat these steroids tremendously valuable as they are in selected cases of certain dermatoses should never be used indiscriminately They should not be given to patients with ordinarily nonfatal chronic dermatoses or with the common allergic dermatoses unless and until the other less dangerous available dermatologic measures have been tried and have proved inadequate

Since the dangers of ill effects are so obviously the sole limiting

factors preventing the more widespread and general use of adrenal steroid hormones in dermatologic therapy two relatively recent advances are to be hailed with great satisfaction The first of these is the use of local treatment with hydrocortisone * ointments lotions and creams an excellent and effective remedy for a great many common itching and inflamed dermatoses infantile eczemas and adult forms of atopic dermatitis lichenified eczematoid dermatoses and genital pruritus otitis externa acute subacute and chronic eczematous and eczematoid eruptions of many areas including the face eyelids and hands contact dermatitis and eczematous drug eruptions etc[4-7] External applications of hydrocortisone have thus far never been shown to produce serious systemic ill effects even after prolonged use on extensive eruptions Nevertheless even these external applications of the hormone should not generally be relied on alone They should be combined with search for and elimination of causal agents and the selected diagnostic procedures and internal and external remedies appropriate to the condition Used in this way to *supplement* but *not* to *supplant* other effective internal measures and proved topical agents (various kinds of shake lotions ointments or pastes containing Vioform Sterosan diodoquin tars menthol and other antipruritics as well as superficial radiation therapy) hydrocortisone is perhaps the most valuable single external medicament ever introduced into dermatology It brings speedy relief in many cases of a great variety of common dermatoses it does not sting stink or stain and it has not as yet produced a single instance of either systemic ill effects or allergic sensitization dermatitis—truly a remarkable record and cause for optimistic appraisal of its future

The second recent advance—one which promises to have if not greater then at least more general value than the introduction of topical preparations of hydrocortisone—is the fact that chemists have now been able to juggle the basic steroid molecules of the naturally occurring adrenocortical hormones and shift about lop off and add various groups side chains and chemical elements in such ways as to come up with steroid relatives in which one or another biologic property of the natural hormones is much reduced or is eliminated another property much intensified etc

Thus we now know that hydrocortisone systemically will do practically everything that cortisone will do systemically and will require a somewhat smaller amount (a ratio of about 4 5) to achieve the same effects Therefore all my previous remarks regarding systemic

* Hydrocortisone is used here in the generic sense to include all topically effective and safe steroid relatives and derivatives

use of cortisone apply to hydrocortisone as well with the necessary 20 per cent adjustment downward in the dosage figures for the derivative We also know that cortisone is therapeutically almost ineffective on external application to the skin while hydrocortisone is very effective and that in turn about one tenth the amount of topical fluorohydrocortisone will produce the same local therapeutic effects as the tenfold amount of externally applied hydrocortisone It is also known that fluorohydrocortisone and aldosterone have a tremendously increased effect on sodium chloride and water retention while the newer steroid relatives metacortandracin (prednisone) and metacortandralone (prednisolone) have much less effect than cortisone on the retention of salt and water although in our experience they have a greater tendency to produce moon facies buffalo humps and presternal and clavicular pads

This short sketch of some recent molecule magic must suffice to show how the wizardry of the organic chemist by producing the relatives and companions of naturally occurring steroid hormones has already given us medicaments which will reduce to a large degree one of the limiting undesirable effects of the systemic administration of the older steroids in dermatologic therapy namely the retention of sodium chloride and water and its sometimes disastrous consequences

It appears not altogether unreasonable therefore to hope that we may someday perhaps soon have at our command steroid medicaments (not necessarily naturally occurring hormones) which will have a minimum of ulcerogenic effects hypertensive effects harmful psychic effects diabetogenic effects and other undesirable activities and yet retain augmented or unimpaired their tremendous therapeutic powers to help the unnumbered hosts of sufferers from many allergic and other skin diseases (see also Chap 57)

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diseases are quite dissimilar The vascular changes in periarteritis are essentially cellular inflammatory lesions in and adjacent to the walls of small and medium sized arteries and hypertension is common When renal insufficiency occurs in periarteritis it is the end result of multiple infarctions of renal parenchyma caused by thrombotic occlusion of many diseased arteries

The wire loop lesions seen in the glomeruli in many cases of lupus erythematosus do not occur in periarteritis In lupus erythematosus small arteriolar and capillary lesions are often most intense in the kidneys although they occur in other organs and tissues Microscopic hematuria is invariably present and renal insufficiency supervenes when the arteriolar lesions and the glomerulitis are sufficiently diffuse and severe to be equivalent to or identical with diffuse glomerulonephritis Only then terminally is mild hypertension occasionally observed

Both in periarteritis and in lupus erythematosus the multiplicity of vascular lesions throughout the body accounts for the occurrence of symptoms and signs in many diverse organs and structures In fact this characteristic multiplicity of symptoms and signs in many parts of the body first enables the clinician to suspect the diagnosis If there is eosinophilia involvement of peripheral nerves or hypertension the possibility of periarteritis is enhanced In contrast the most conspicuous symptoms and signs of lupus erythematosus are centered in the joints the blood the kidneys and the skin In rheumatoid arthritis they are centered predominantly in the joints in rheumatic fever in the heart and in scleroderma in the skin and esophagus

Purpuric skin lesions may occur in periarteritis and in lupus erythematosus as a result of the rupture of superficial capillaries They may resemble the purpura observed in some fulminating allergic or anaphylactic states However the more common type of generalized purpura observed in lupus erythematosus is due to thrombocytopenia rather than to capillary fragility Thrombocytopenia and acquired hemolytic anemia which occur in lupus erythematosus are not characteristic of any of the other collagen diseases or of allergy Nor do they show the LE blood phenomena of lupus erythematosus

An auto immune phenomenon is involved in lupus erythematosus but only in periarteritis nodosa has an exogenous allergic etiology been proved It is the one member of the collagen group in which esinophilia is commonly observed in the active stage of the disease Absence of eosinophilia at any stage of the disease is unusual About one third of the patients with periarteritis have previously had asthma Many have previously had urticaria or other allergic phe

nomena or they exhibit such symptoms with the onset of the disease If the disease has an acute fulminating onset it may at first resemble acute anaphylaxis or serum sickness including at times a widespread purpuric rash due to rupture of fragile skin capillaries Finally typical vascular lesions of periarteritis nodosa have been reproduced in animals by the repeated intravenous injection of foreign protein The puzzling feature is that it is rarely possible in human beings to determine the nature of the offending antigen

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36 | *Ely Perlman*

CENTRAL NERVOUS SYSTEM ALLERGY

Allergy is considered to play a role in a variety of neurologic symptoms and symptom complexes In certain instances some symptoms are unquestionably due to allergic reactions and can be reproduced at will by exposure of the patient to the offending allergen(s) Some neurologic syndromes such as migraine or Menière's disease are known to be caused by allergic reactions in a certain percentage of cases Still others most notably multiple sclerosis have been suspected of having an allergic etiology but the evidence is not conclusive

Central nervous system symptoms which have been described after exposure to known allergens are numerous and varied depending on the pathogenesis and the localization of the reaction They may be *mild and brief or severe generalized and prolonged* The list of symptoms which have been definitely induced by allergic mechanisms includes weakness tremor tinnitus vertigo deafness nystagmus scotomas hemianopsia blurring vision blindness ptosis irregularity of pupils photophobia speech disorders including aphasia excitability anxiety confusion insomnia somnolence stupor convulsions encephalopathy coma ataxia localized paralysis hemiplegia and others

The pathogenesis of these symptoms is difficult to prove because it is not amenable to study in most instances It is likely that the mechanisms ascribed to other allergies apply to those of the central nervous system Cerebral edema local or diffuse is probably similar to the urticarial type of reaction and is the most plausible ex

planation of many of the manifestations of central nervous system allergies. There is considerable clinical evidence to support this concept. Other types of allergic reactions are based on vascular changes such as capillary dilation, allergic inflammation, purpura, and vascular occlusions whether spastic, hemorrhagic, or thrombotic. These types of reactions have been suspected but have not been proved to be operative in allergic neurologic disorders. Primary demyelination, such as occurs in multiple sclerosis, has no counterpart in other clinical allergies but is regarded as being caused by allergic reactions because it has been produced by immunologic technics in experimental animals.

Almost all of a large variety of allergens have been shown to cause one or another of the central nervous system disorders. Foods, drugs, and injectables are the commonest allergens, while inhalants and contactants, which are prominent in other allergies, play a negligible role in these cases. Among foods the commonest offending allergens are milk, chocolate, eggs, and shellfish. Much of the early evidence suggesting this allergic cause of central nervous system symptoms was accumulated at the time when vaccines and foreign serums (antitoxins) came into wide use. Other injectables, such as liver extract, insulin, and bee venom, also have been reported as the cause of such reactions. Various drugs have been suspected, the most significant being nirvanol, sulfonamides, arsenic, and quinine. Infections, bacterial and viral, have been suspected of causing encephalomyelitis on an allergic basis, but the evidence is incomplete. Cases resulting from killed bacterial vaccines and toxins also have been reported and are suggestive although not conclusive in most instances.

The clinical description of neurologic symptoms based on allergic reactions began toward the end of the last century when Osler[1] reported three cases of hemiplegia following vaccination. Peripheral neuritis after foreign serum injections was described as early as 1897 and was reviewed by Pollet. Optic neuritis during serum sickness was described in 1922, and unusual somnolence associated with an allergic reaction was reported in 1923.[3, 4] In the same year cases of Ménière's disease were ascribed to allergic reaction to foods.[5] In 1928 Kennedy[6] reported meningeal and focal lesions causing hemiplegia, aphasia, hemianopsia, and marked papilledema during serum sickness. Allergic headache from food was reported in 1930 by Fyermann,[7] who also described several cases due to inhalant allergens. In 1933 typhoid vaccine was reported as causing an acute ascending polyneuritis.[8] In 1935 reports of two cases of encephalomyelitis following the use of serum or vaccine were published, one of which came to autopsy.[9] A case of encephalitis after yellow fever

vaccination came to autopsy in 1936[10] The lesions found resembled those of multiple sclerosis and suggested the possible allergic etiology of this disease[11] In the same year other investigators[1] were similarly impressed with this possibility In 1938 a case of violent convulsions following the ingestion of chocolate was described[13]

This brief historical review points out the range and variety of clinical neurologic disturbances which can be caused by allergic reactions Experimental evidence to support these observations has been reported Local brain lesions of both the Arthus and the general anaphylactic type were produced in dogs and rabbits as early as 1931[14, 16] This type of reaction was studied extensively and was reviewed by Ferraro[17] In 1943 Jervis[18] found that the injection of Forssman antibodies into the carotid arteries of guinea pigs caused ataxia and nystagmus He observed diffuse degeneration of neurons a mild glial reaction and foci of demyelination The experimental studies on the immunopathogenesis of lesions resembling multiple sclerosis actually began with the use of rabies vaccine (reviewed by Hurst)[19] It was soon found that brain tissue and not the virus itself was responsible for the lesions produced Subsequent studies using prolonged injections of brain tissue in monkeys produced more consistent results[20-22] The regular and consistent production of paralyses was finally achieved by the use of Freund's[23] adjuvant by Morgan[24] and other investigators[25] It is certain that brain tissue is organ specific and not species specific The antigen is most abundant in the white matter of the brain and appears to be a lipoprotein[6, 7]

It is apparent from the foregoing that a wide assortment of neurologic symptoms can be produced by allergic reactions There are a number of central nervous system disease *syndromes* which in some cases have been shown to be due to an allergic mechanism This has been possible because in some instances the disease occurs only in association with other obvious allergic manifestations and in some cases it can be consistently reproduced by exposure to the offending substance

Migraine is a well established symptom complex which in most cases is due to a multiplicity of factors Endocrine neurogenic and psychogenic factors as well as foci of infection have been implicated[9] However a certain percentage of the cases are due solely to allergy This was first suggested in 1919[9] and soon was well established by the reports of many observers[30-34] The allergic etiology of other types of headache[7, 3] including atypical migraine was extensively reviewed by Friedman and Von Storch[36] Foods and drugs are the commonest offenders but inhalants also have been implicated[37]

The deafness tinnitus and vertigo of *Meniere s disease* can be caused by a variety of factors including metabolic dyscrasias vasomotor influences arteriosclerosis foci of infection and systemic disease resulting in hydrolabyrinthitis Here again the cause in a small portion of the patients is clearly allergy generally to foods although other types of allergens including inhalants may be responsible Duke[5] was among the first to observe this syndrome which occurred after the ingestion of pears spinach plums and wine or the injection of their extracts Other observers contributed further clinical evidence for the allergic etiology of Méniere s syndrome[39-40]

Idiopathic epilepsy is another neurologic disorder of unknown etiology in which allergy has been suspected of playing a part In this condition also the majority of cases cannot be ascribed to allergy but there is little doubt that some of them are due to allergy especially in view of the striking cases that have been reported As early as 1919 a case of epilepsy of six years duration was described[41] which was finally traced to chocolate A well known and well established case of chocolate allergy resulting in convulsions was reported by Pardee[13] and others have been collected and reported by Clarke[4] The most extensive and critical review of the subject is that of Davison[43]

Multiple sclerosis is another entity for which an allergic pathogenesis has been suspected Some of the experimental evidence has been discussed previously and most of this is based upon brain tissue antibodies (see Chap 6) There are however a number of observers who have considered food allergies to play a role in this disease[44 45] The evidence is not conclusive that either type of allergic reaction can cause the disease

Prigal[46] has reviewed the relationship between allergy and multiple sclerosis and found the experimental evidence indicative of an allergic mechanism but this cannot be confirmed clinically Autosensitivity and self perpetuating mechanisms are possibly involved

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37

OPHTHALMIC ALLERGY

A classification of allergic diseases of the eye may be based on the route of sensitization the type of antigen or the type of reaction This is well recognized by ophthalmologists[1] as well as allergists[3] who consider the appearance of the lesions as only one of the many features in the classification of allergic diseases of the conjunctiva cornea and sclera

The route of the sensitizing and of the reactive dose may be (1) by direct contact (cosmetics pollens chemicals) (2) air borne (pollens cosmetics) (3) via the blood following ingestion or injection (foods drugs antibiotics) or (4) by lymphatic spread from other sites (infection in sinuses or teeth) Any combination of routes may occur for the sensitization and the allergic reaction For example an individual may be sensitized with sulfathiazole by ingestion and at a later date develop a local reaction when the ointment is applied to the eyelid or conjunctival sac On the other hand sensitization may first be produced by contact of the ointment with the lid or conjunctival sac and at a later date following ingestion the allergic reaction may occur locally where the ointment had previously been applied

The variety of potential allergens is almost limitless In general any protein or substance capable of combining with body protein to become a protein complex may be allergenic In establishing a diagnosis therefore a careful history is extremely important It should include consideration of temporal geographic and dietary factors as well as detailed information concerning the use of drugs

cosmetics lotions soaps and the like both by the patient and by the family

Allergic diseases of the eye may be classified anatomically as follows

- Extraocular lesions
  - Acute allergic conjunctivitis
  - Chronic allergic conjunctivitis
  - Eczema of eyelids
  - Angioedema of eyelids
- Vernal catarrh
- Ocular lesions
  - Cornea
    - Phlyctenular keratoconjunctivitis
    - Recurrent marginal ulcers
  - Uveal tract
    - Nongranulomatous uveitis
    - Granulomatous uveitis
    - Sympathetic ophthalmia
    - Endophthalmitis phacoanaphylactica
  - Lens Cataract

Although anatomic classification of allergic reactions is less useful to the allergist in establishing a diagnosis the location and appearance of the lesion are of distinct value in pointing toward certain lines of investigation Not all the lesions listed have been clearly proved to be allergic Nor is this listing inclusive of all eye diseases ascribed at one time or another to allergic causes The following discussion will emphasize those conditions most commonly seen by the allergist rather than the ophthalmologist

Of the extraocular lesions the most common are the *acute and chronic conjunctival allergic reactions* characterized by chemosis itching and profuse tearing These are most likely due to air borne allergens or to eye medicaments less commonly to foods The severity rate and time of recurrence depend on the nature and distribution of the offending allergen There are usually no signs or symptoms between attacks of acute allergic conjunctivitis Almost always with conjunctivitis due to pollen allergy there is an associated allergic rhinitis As with the nasal secretions in allergic rhinitis the secretions or scrapings from the conjunctiva in allergic conjunctivitis reveal eosinophilia a valuable diagnostic aid particularly helpful in distinguishing allergic from infectious conjunctivitis [4]

Eczematous reactions of the lids are characterized by dry scaly hyperemic lesions which sometimes become moist They are most likely to be caused by contactants sometimes by way of the hands Nail polish is a frequent cause and wool is occasionally implicated while various topically applied drugs and antibiotics are not in

frequent causes Face powder has become less important since the major offenders orris root and rice powder are now less commonly used in its preparation Other cosmetics lotions and creams are all potential offenders Air borne inhalants may rarely cause eczema of the lids sometimes in association with acute allergic conjunctivitis Food allergy is not likely to cause eczema of the lids unless associated with eczema at other sites as well Occasionally eczema of the lids is associated with infection in the conjunctiva or in foci nearby such as the upper respiratory tract and sinuses This will be discussed below

Angioedema characterized by severe swelling of the lids may be associated with swelling of the lips mouth tongue and glottis or with other manifestations of generalized urticaria Itching is usually but not always present This type of reaction is generally associated with blood borne allergens following injection or ingestion It is uncommonly related to contact or inhalant allergy

Vernal catarrh has been placed in a separate category because it has both extraocular and ocular lesions Considerable doubt has been expressed concerning its allergic etiology particularly in relation to pollenosis The conjunctiva in vernal catarrh is described as having a cobblestone appearance due to mucosal proliferation resulting in flat polygonal papillae usually in the tarsus of the upper lid and in severe cases in the lower lid The conjunctiva is covered with a sticky pseudomembrane which may be peeled off without causing bleeding Lesions of the limbus and cornea are also described While there tends to be a seasonal relationship between exacerbations of the lesions and the various pollen seasons a residual permanent lesion usually remains long after the pollen season While a high percentage of these patients show positive skin reactions to one or many pollens treatment with injections of pollen extracts has been notoriously unsuccessful Furthermore vernal catarrh has been observed in patients who are in pollen free areas and it has been suggested that the lesions are due to a hyperreactivity to ultra violet radiation or other physical factors rather than to allergic disease However the dense eosinophilia in the secretions from vernal catarrh continues to serve as evidence in favor of an allergic etiology

Many of the ocular diseases have been thought to be due to allergic mechanisms These include various forms of keratitis uveitis sympathetic ophthalmia endophthalmitis and cataract The experimental and clinical evidence suggesting the allergic etiology of these ocular diseases has been reviewed by Woods[1 5] In brief the offending allergens have been of two major types (1) bacteria or bacterial products and (2) autoantigens produced by breakdown of

tissue proteins such as lens protein or uveal pigment The possibility of allergy to bacterial antigens lends importance to a diligent search for foci of infection in uveitis while the concept of autosensitivity is the rationale for prompt enucleation in certain cases of perforating injuries of the eye to prevent sympathetic ophthalmia Autosensitization has also been proposed as a possible cause of cataract

Regarding the role of bacteria in diseases of the eye it is generally agreed that there is a relationship between bacteria and various diseases of the eye but there is disagreement as to whether these diseases are due to allergy to bacterial substances or to primary toxicity The answer probably lies somewhere between the two extreme viewpoints While primary infection and toxicity can cause lesions indistinguishable from allergic reactions truly allergic reactions to bacterial substances can and do occur Two cases are worthy of mention as examples of infection and bacterial allergy respectively The first is an example of periorbital dermatitis indistinguishable from allergic eczema probably due to staphylococcal infection

A fifty year old housewife was seen because of a ten month history of alternating eczematoid dermatitis around the eyelids and orbit All the usual treatments including cortisone locally and systemically were ineffective A smear examination of pus from the left conjunctival sac revealed polymorphonuclear cells with occasional eosinophils Extensive intradermal tests showed only slight reactions to dust feathers and a few molds Antral lavage resulted in removal of pus and shreds from both antrums Within two days the eczematoid dermatitis around the eyelids had almost completely cleared and she was well thereafter for ten months except for recurrences associated with upper respiratory infections and sinusitis which cleared promptly following treatment with antibiotics or lavage of the antrums or both She discontinued medical management against advice because her skin had cleared up and she saw no reason to return

This case emphasizes the need to consider the primary toxic effects of infection before making a diagnosis of allergic disease The preponderance of neutrophils in the secretions and the absence of positive skin reactions to various vaccines and toxoids led to a diagnosis of infection rather than allergy

The second case is an example of uveitis probably due to bacterial allergy

A thirty four year old man was first seen March 1951 because of loss of vision over a seven year period In March 1947 he developed progressive loss of vision in the left eye until his acuity was an uncorrectible 20/400 In March 1952 he developed the same condition in the right eye which again progressed until his vision was stated to be 20/100

Treatment had consisted of corticosteroids many broad spectrum antibiotics and foreign protein and typhoid therapy An allergy work up in 1953 revealed positive reactions to house dust horse epithelium and catarrhal vaccine and he was treated with dust and vaccine for a few months without relief No particular treatment had been directed toward his sinuses although x rays were said to have shown sinus disease

The physical examination revealed bilateral uveitis with corneal opacities partial in the right and complete in the left Visual acuity was 20/200 in the right eye and nil except for light in the left

In March 1954 he was tested with various bacteriologicals with marked immediate positive reactions to staphylococcus ambotoxoid (Squibb) and slightly less but distinctly positive reactions to staphylococcus toxoid (Lederle) and to an extract of an *aureus* strain of *Staphylococcus* (FIO) which was under investigation in our laboratories The following day on a routine visit to his ophthalmologist he was found to have even greater positive reactions at the *Staphylococcus* test sites on his arms and in addition had an acute uveitis plus an optic neuritis in his right eye He was hospitalized placed on ACTH therapy and had a bilateral radical sinusotomy He was started on bacterial antigen therapy with injections of the materials to which there were positive reactions beginning with high dilutions Culture of the tissue removed from his sinuses revealed only *Streptococcus viridans* but unfortunately he had been given antibiotics prior to surgery

Following discharge from the hospital his vision was 20/70 in his good eye He was continued on ACTH therapy for a few months then changed to hydrocortisone which was gradually tapered in dosage to 5 mg a day by March 1956 Vaccine therapy was continued He improved progressively attaining 20/30 vision without correction in the right eye In March 1957 he elected to discontinue vaccine therapy and in March 1959 steroids were discontinued When seen by the ophthalmologist in August 1959 vision was 20 25 in the right eye

This case is better explained on an allergic than an infectious basis for the following reasons (1) There were immediate and delayed positive reactions to skin tests with bacterial products (2) These were followed by a flare up of his disease thus demonstrating a constitutional reaction (3) Removal of the focus of infection in the sinuses and treatment with vaccine were followed by progressive improvement in his vision and quiescense of his disease despite reduction and ultimate cessation of corticosteroids (See also discussion on uveitis Chap 6)

The skin test is an extremely important diagnostic tool in allergic disorders of the eye In general patch tests are best for cosmetics and other contactants scratch tests and intradermal tests are best used for foods and inhalants There are those who recommend the use of conjunctival tests that is placing extracts of allergens in the

conjunctival sac and reading the positive reactions on the basis of suffusion and edema of the conjunctiva While these tests have been of interest from the standpoint of investigation they are of less practical value since one is limited in the number of tests one can do at a time and they may be dangerous to the eye in violently positive reactions

Those who are particularly interested in the problem of bacterial hypersensitivity also make *skin tests* with various materials derived from bacteria These may be grouped roughly into solutions and suspensions The solutions may be of either extracellular (culture filtrates) or intracellular (ground or lysed organisms) origin while the suspensions are only intracellular (vaccines) The intradermal tests with these materials should be read at fifteen or twenty minutes and again in twenty four to forty eight hours Solutions may give either immediate or delayed reactions or both but a positive *reaction to a well washed fresh vaccine is more often of the de*layed type

The significance of positive skin reactions to bacterial antigens is obscured by the toxic properties of many of these antigens if used in high concentrations If a strongly positive reaction to a low concentration of bacteria or bacterial product can be correlated with the clinical picture it merits respect and may be useful in considering vaccine therapy discussed below

The treatment of allergic diseases of the eye like that of allergic diseases in general may proceed when the diagnosis is established The most effective and complete cures of allergic reactions are obtained in those patients in whom the offending allergen can be removed Unfortunately such cases are far outnumbered by those in which the allergen can be eliminated only partly if at all as with pollens air borne molds dust and bacteria In these cases other measures must also be used

Symptomatic and palliative measures are too numerous to detail here Epinephrine 0 2 or 0 3 ml given subcutaneously is *helpful* in acute angioedema It is much better to give these small doses repeatedly every twenty to thirty minutes than to give a large dose initially from the standpoints both of therapeutic effect and of minimizing the side effects of excitability and cardiovascular disturbances Ephedrine 3/8 grain and Amytal 3/4 grain three times a day are helpful The antihistamines described in detail in Chap 58 are also useful medications When there are conjunctival reactions Neo Synephrine 1/8 per cent or collyrium drops are helpful in the mildest cases in addition to ephedrine and antihistamines and in the more severe problems topical hydrocortisone ointment

or drops together with neomycin if there is any danger of infection may be used However since an abscess in the anterior chamber of the eye may follow the use of hydrocortisone or cortisone ointment or drops even when antibiotics are used at the same time these hormones should be used only when more conservative treatment has failed and preferably not until the patient has been seen by an ophthalmologist Of particular danger is the use of steroids in unrecognized herpes simplex of the cornea since these lesions progress rapidly even to blindness in the presence of steroids

In the final analysis allergists find the most important approach to inhalant type allergy (pollen mold dust) to be immunization against these materials by injections of extracts in an attempt to build up tissue and circulating antibody which will combine with and inactivate the antigen This statement is oversimplified since there is much yet to be learned about the mechanisms involved in the relationship of immunity to allergy but in pollinosis this treatment has stood the test of time since most allergists give high figures for improvement with this method The specific dosage schedules and other details are discussed in Chaps 16 and 56

In ocular allergy since the most likely offending allergen is bacterial or autoantigenic treatment consists first in a careful search for and elimination of foci of infection particularly in the nose throat sinuses and teeth Appropriate antibiotics should be used in conjunction with surgery or where foci cannot be removed

ACTH and corticosteroids have assumed considerable importance in the treatment of ocular diseases under discussion since their palliative if not their curative effects are unquestioned

Local treatment with cortisone and its analogues is effective for external diseases of the eye while ACTH parenterally and cortisone and its analogues are helpful in cases of uveitis Forty units of ACTH by slow intravenous drip or ACTH gel 40 units intramuscularly or subcutaneously twice a day are preferred by many ophthalmologists in the early stages of treatment of uveitis Of the orally administered cortisone analogues Prednisone or Prednisolone seem to be favored at the present time These are approximately equal in potency and the dosage while depending upon the clinical course may begin as high as 40 mgs a day in four divided doses Later the dose is tapered off but where necessary the hormone may be continued for a long period of time as in case 2 above

The dangers and precautions of prolonged steroid therapy are discussed in Chaps 34 and 57

Vaccine therapy is employed by some scorned by others Its value has been neither proved nor clearly disproved since carefully con

trolled clinical studies in such diseases as uveitis are virtually impossible Dramatic cures of uveitis have occasionally followed removal of a focus of infection without vaccine therapy—as without any other therapy for that matter

Recognizing the lack of proof of benefit from vaccine therapy it is the author s opinion that vaccines should be used *in the hope* that they may be of value in such patients This is particularly true in patients with positive skin reactions to certain of the intracellular and extracellular materials derived from various types of organisms and in patients with positive skin reactions to autogenous vaccines derived from foci of infection On the other hand in patients with no apparent focus of infection and with negative skin tests there is less justification for vaccine therapy

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Kurt Lange

38

ALLERGY AND DISEASES OF THE KIDNEY

As early as 1907 Schick [1] suggested that acute glomerulonephritis might be due to an antigen antibody reaction Many other clinical observers since then have followed this trend of thought which was based mostly on circumstantial evidence

There is a constant time interval of seven to fifteen days between the initial sore throat and the first signs and symptoms of acute glomerulonephritis an interval which is best explained by the time necessary for antibodies to some streptococcal antigen to be formed and to be released into the circulation Despite intensive search streptococci have never been found in the kidneys of these patients It must be assumed that the streptococcus releases some antigen which stimulates antibody formation and which at the same time localizes on the glomerulus possibly in the process of excretion The edema in acute glomerulonephritis as well as in nephrosis is diffuse and cannot be explained by purely renal factors It resembles especially in the nephrotic stage the edema seen in acute allergic conditions such as serum sickness drug sensitivities and trichinosis The periorbital swelling is most prominent the edema is diffuse and not dependent to any great extent While the interval between the initial throat infection and the onset of the renal disease as mentioned varies between seven and fifteen days reinfections lead to severe aggravations within two days an interval which is typical for an immunologic anamnestic reaction or recall phenomenon

In the nephrotic stage of glomerulonephritis and the so-called

pure nephrosis high eosinophil counts are common They return to normal during remissions and recur with relapses [3] The incidence of allergic manifestations in individuals with nephrosis is high [4, 5]

In addition to this more or less circumstantial evidence the hypothesis was further substantiated by Masugi [6] who produced a disease in the rabbit which clinically immunologically and morphologically closely resembled human glomerulonephritis This was accomplished by injecting rabbits with serums taken from ducks which were previously immunized with rabbit kidney emulsion The injection of

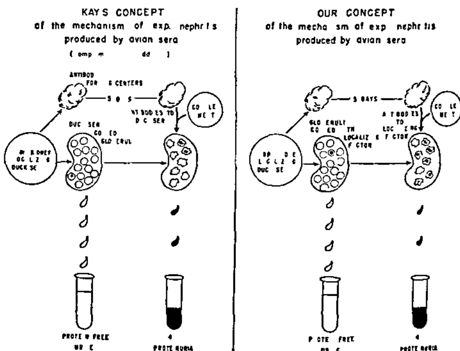


Fig 38 1 Scheme of action of rabbit kidney localizing duck serum

this anti-rabbit kidney duck serum into rabbits produced after an interval of at least five days all the signs and symptoms of acute glomerulonephritis which subsequently followed through the typical stages of the human disease

In this experimental disease immediately on intravenous injection the anti-rabbit kidney duck serum localized in the glomerular membrane as demonstrated by radioactive labeling (Fig 38 1) [7] Since it is avian serum complement is not drawn into the antigen antibody reaction and tissue destruction does not occur The rabbit however forms its own antibodies to the localizing factor of the in

jected foreign protein the duck serum When these antibodies appear in the circulation an antigen antibody reaction takes place in which the antibodies against the localizing factor of the duck serum react with the duck serum antigens previously localized in the glomeruli[8] Complement (C') is used in large amounts in this purely mammalian antigen antibody reaction and an active tissue destroying glomerulonephritis results This animal disease can serve as a model of the human disease and all therapeutic measures successful in the treatment of the human disease have likewise proved successful in the treatment of this animal disease[9]

Finally a good deal of direct evidence was obtained when it was found that in all cases of acute glomerulonephritis and in almost all cases with the nephrotic syndrome serum complement levels (C') were low[10]

The role of C' in antigen antibody reactions as we understand it today requires some explanation From radioactive and fluorescent tracer studies it is well known that antigen and antibody can unite without the presence of C' Available evidence however seems to indicate that tissue destruction or alteration can only take place in the presence of C'

An interesting experiment which parallels the immunologic mechanism of glomerulonephritis was carried out by Adler[11] He incubated sheep erythrocytes with human gamma globulin then washed the cells free of all nonadherent globulin by several saline washings and added an antiserum containing antibodies against human gamma globulin No hemolysis occurred The addition of small amounts of C' however resulted in lysis of the sheep erythrocytes No anti-sheep cell hemolysin was used in this reaction In other words the red cell lysis resulted from the fact that the red cells were coated with human gamma globulin to which an antibody was added in the presence of C'

The amount of C' used in an antigen antibody reaction depends on the surface area of the antigen provided that sufficient antibody is available It will thus be understood that in common bacterial or viral infections the over all C' level is not lowered since the total surface area of the invading bacteria is a few square centimeters at most However when a large surface like the glomerular surface approximately 1 square meter in size becomes antigenic huge amounts of C' are used The body is not able to replenish C' fast enough resulting in a fall in the over all C' level Thus C' levels become an indirect indicator of the presence or absence of antigen antibody reactions on large surfaces provided that formation of C' is not impaired or that C' is not lost in the urine or destroyed by other mech

anisms Such factors could be excluded however in numerous experiments in patients with glomerulonephritis and nephrosis[12]

In the typical allergic antigen antibody reaction the antibody is sessile while the antigen is introduced in minute amounts thus giving only a very small surface of interaction which does not require large pool depleting amounts of C′ By contrast however in nephritis and nephrosis the antigen is sessile and the antibody is newly formed and reacts with the large antigenic surface Therefore in acute glomerulonephritis the titers of C′ will always be low (Fig 38 2) With the method the author uses the normal values vary be

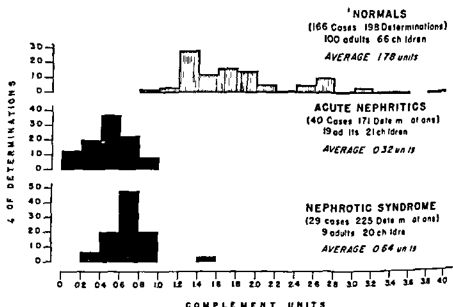


Fig 38 2 Distribution of average complement content in normal persons acute nephritic patients and patients with the nephrotic syndrome

tween 1 2 and 3 units with an average value of 1 78 units while in the patients with glomerulonephritis the titers vary between 0 and 1 unit with an average of 0 32 units

In the author s group of 165 cases of acute glomerulonephritis there has not yet been a single case which did not have an abnormally low C level The C titer thus becomes a significant test in the differential diagnosis of hematuria There is a concurrent rise in the C level to normal on the return of the clinical and laboratory findings to normal This is the most commonly encountered course of the disease

If the acute glomerulonephritis develops into the subacute stage however the antigen antibody reaction persists the C may stay low and the disease will progress until more and more glomerular tissue has been destroyed and death from uremia results Conversely immunologic healing with return of C to normal may occur but so much functioning tissue may have been lost in the first attack that the patient will not tolerate further loss of functioning kidney tissue which may occur as a result of arteriosclerosis in the normal aging process The end result is a slowly developing uremia occurring twenty to thirty years after a burned out nephritis a term which should replace the misleading designation chronic glomerulonephritis

The glomerulus in nephrosis is severely damaged in a similar manner (but probably with a mechanism of coating with different antigens) as a result of an antigen antibody reaction Electron microscopy shows numerous vesicles in the cytoplasm of the epithelial cells of the glomerulus and changes in the podocytes of the epithelial cells [13] When the syndrome suddenly clears up under the influence of corticosteroids which suppress antibody formation these cellular changes disappear and massive diuresis occurs Such a diuresis occurs whether or not there is a rise in the serum proteins This makes it highly improbable that the low osmotic serum pressure so often accused of being the cause of the edema is the only or most important reason for the fluid accumulation We have to assume that the antigen antibody reaction in the nephrotic syndrome is not confined to the capillaries of the glomerulus but extends to the capillaries throughout the body leading to an increased permeability While C is low during the edematous phase in over 80 per cent of patients with nephrosis there is a trend toward normal or normal levels are reached prior to diuresis whether this is a spontaneous remission or a corticosteroid induced remission

Thirteen spontaneous remissions in patients with nephrosis were observed All were preceded by a rise of the subnormal serum complement levels toward or to normal twenty four to seventy two hours prior to the onset of diuresis These spontaneous remissions with massive diuresis were preceded in 11 of the 13 instances by an infectious disease with marked rise in temperature five to twelve days prior to the spontaneous remission In four children a total eosinophil count prior to the episode of fever was found to be within the normal range of 100 to 300 per cu mm During the episode of high fever the eosinophil count fell from a normal level in these four instances to below 11 per cu mm In one child 17 ketosteroids in the urine were determined a sharp rise to values above normal

was noted during the episode of fever Similar findings were recently reported by Klein *et al* [14] It thus becomes probable that spontaneous remissions often are produced by a stress situation with production of huge amounts of ACTH Shortly prior to relapses C′ again falls to subnormal levels

The role of ACTH and cortisone in inducing a remission of the disease can be exemplified in nephrosis induced in the rabbit by anti-rabbit kidney duck serum A typical example of one control animal

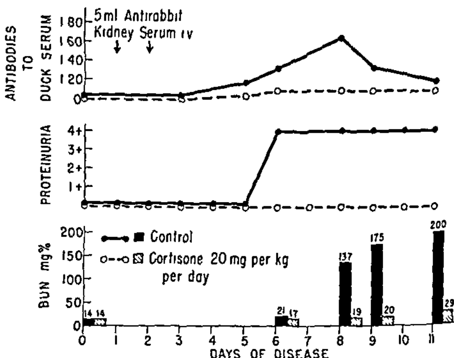


Fig 38 3 Representative examples of the course of antibody titers proteinuria and blood urea nitrogen levels in two rabbits injected with rabbit kidney localizing duck serum with and without cortisone treatment

and one cortisone treated animal is shown in Fig 38 3 It will be noted that the cortisone which was given during the development of nephrosis prevented antibody formation which was very intense in the control animals In the cortisone treated animals proteinuria was absent or mild blood urea nitrogen rose only slightly and the disease was either suppressed or markedly ameliorated These two examples were selected at random from 83 animals thus studied

Similarly in the human disease after eight to fifteen days of

therapy with huge amounts of steroids a sudden diuresis occurred simultaneously with the return of C to normal When the check reins on antibody formation—the steroids—were not applied any longer antibody formation was rapidly resumed and relapses oc curred in a high percentage of cases Thus it became imperative to devise a scheme of steroid therapy which would continuously de press antibody formation sufficiently but would not lead to a Cush

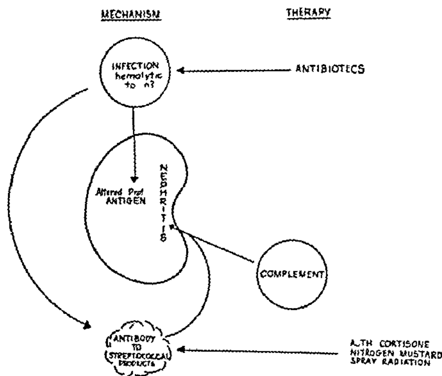


Fig 38-4 Scheme of probable immunologic mechanisms of glomerulonephritis

ing syndrome *Such a therapeutic scheme* based on immunologic considerations was developed After the initial diuresis was induced by ACTH large amounts of cortisone were given for three con secutive days out of each week followed by four days of steroid abstinence This was repeated for three days each week for at least one year A total of 51 cases were treated with this therapeutic regime by the author and his associates during a period of six years The re sult was gratifying There was only one death in the entire group

This group observed for an average period of thirty one and one half months was compared by the life table statistical method to a group of nephrotic subjects who were not treated with steroid maintenance The *expected* mortality in the treated group on the basis of the mortality in the nontreated group was 12 8 deaths In the treated group however only one death occurred ($p<0\,001$) When nitrogen mustard was given instead of corticosteroids an identical course of remission and relapse with an identical behavior

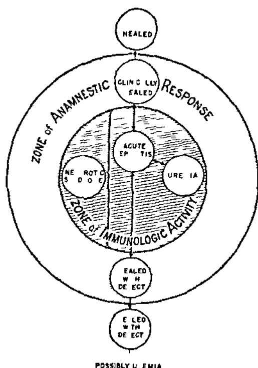


Fig 38 5 Scheme of the probable relationship between immunologic factors and clinical course of glomerulonephritis and the nephrotic syndrome

of C was observed Since the only common denominator between corticosteroids and nitrogen mustard is their strong antibody suppressing effect we have further evidence of the antigen antibody mechanism of nephrosis

Most recently Mellors and Ortega [15] have produced direct proof indicating that the hypothesis of an immunologic mechanism is correct They have produced fluorescein labeled antisera to human gamma globulin With these sera they were able to show that in human autopsy material taken from patients suffering from glo-

merulonephritis and the nephrotic syndrome gamma globulin the carrier of antibodies was localized in large amounts in the basement membrane of the glomerulus In the normal kidney or in other nephropathies this was not the case

It thus appears that in glomerulonephritis and nephrosis we are dealing with an immunologic mechanism as illustrated in Fig 38-4 In nephrosis however antigens other than streptococci must be considered as pathogenic

The clinical characteristics of these diseases may be well fitted into the immunologic scheme shown in Fig 38 5

There can be no doubt that there are numerous points in this picture which require further study As a working theory it has proved fruitful and stimulating

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39 | *Joseph Harkavy*

ALLERGIC FACTORS IN CARDIOVASCULAR DISEASE

Experimental evidence of specific hypersensitivity of the cardiovascular system is to be found in the immediate and delayed forms of anaphylaxis in sensitized animals (Chaps 1 and 2)

PART I IMMEDIATE REVERSIBLE REACTIONS

Pathophysiology In acute anaphylaxis the immediate reactions are characterized by arteriolar spasm and increased capillary permeability involving arteries and veins irrespective of the influence of blood pressure or nerves [1] Electrocardiograms by means of direct leads of the isolated heart removed from serum sensitized guinea pigs reveal acceleration of the heart alteration in the amplitude of contraction prolonged P R intervals and deviations in RST complexes [2] Other abnormalities consisting of bradycardia tachycardia ventricular extrasystoles auricular fibrillation and bundle branch block have been demonstrated by Miculicich [3] in the rabbit sensitized to egg white and horse serum

That the cardiac muscle per se participates in tissue sensitization and is capable of direct anaphylactic response independent of any alteration in coronary blood flow has been demonstrated by Kellner Penna and Schweid [4] They showed that perfusion of the isolated heart of guinea pigs previously sensitized to crystalline streptococcal proteinase and other agents with specific antigens caused disturbances in impulse formation and conduction in the

form of ectopic beats and A V block of varying degree Similar changes were obtained when the isolated auricular muscle devoid of blood supply was exposed to the specific sensitizing agent

The involvement of peripheral vessels in the anaphylactic reaction is suggested by the development of gangrene of the toes in rats following prolonged sensitization to tobacco Anaphylactic sensitization was demonstrable in these animals by a positive Shultz Dale reaction [5]

In man as in the lower animals the susceptible cardiovascular system may be the seat of allergic reactions These can be acute and reversible in character or delayed Delayed reactions may also be reversible but if untreated may become irreversible

Etiology The exciting agents responsible for sensitization may be inhalants such as pollens foods tobacco drugs and bacterial agents

The etiologic factors and the clinical manifestations of the various reversible forms of cardiovascular reactions are summarized in Table 30

TABLE 30 IMMEDIATE REVERSIBLE FORMS OF CARDIOVASCULAR REACTIONS

Reacting tissues	Clinical manifestations	Exciting agents
Capillaries	Urticaria (hives) angioedema purpura local hemorrhagic necrosis	Inhalants foods pollens drugs and bacteria psychosomatic factors
Peripheral vessels	Migrating phlebitis thromboangiitis obliterans (Buerger s disease) intermittent claudication	Tobacco foods infection drugs
Heart	Disturbance in rate and rhythm such as extra beats tachycardia auricular fibrillation angina pectoris coronary artery disease	Tobacco foods drugs such as salicylates and penicillin pollen immune serums infections physical agents such as cold and heat

Usually irreversible except in the very earliest stages when it may be arrested if smoking is omitted

In a study of 100 patients with coronary artery disease all heavy smokers 44 per cent gave positive reactions to tobacco [7] Positive passive transfer tests for tobacco were obtained in 11 out of 14 cases studied (71 per cent) The positive reacting patients represented a relatively young group averaging forty five years of age Thirty

three per cent of patients with coronary artery disease who reacted to tobacco had a family and personal background of allergy This is about 17 per cent less then that found in patients with asthma Of 140 patients with thromboangiitis obliterans 78 per cent gave positive skin reactions to *tobacco only* when tested in conjunction with other allergens as compared to a mere 9 per cent of a similarly tested group of normal unselected smokers Biopsies of the immediate whealing reactions to tobacco revealed the presence of eosinophils Reagins to tobacco were demonstrable on passive transfer in 44 per cent of 95 cases with positive skin reactions to tobacco

Diagnosis Before attributing any of these cardiovascular conditions to an allergic mechanism it is necessary to exclude organic cardiac and blood vessel disease owing to hypertension rheumatic heart disease arteriosclerosis diabetes or any other known non allergic cause Once this is done the diagnosis of allergy is made on the basis of (1) history (2) physical examination (3) electrocardiographic findings and (4) skin tests The latter must be evaluated clinically before they can be regarded as etiologically related to the presenting symptoms

Treatment The treatment consists of removal of the incriminating allergens with the prospect that the manifestations will disappear completely In cases of urticaria symptomatic therapy may be employed in the form of antihistamines and various steroids such as prednisone ACTH etc The latter are more effective in the acute forms of urticaria and purpura than in the chronic forms (see Chaps 31 and 57)

In conditions in which tobacco has been *proved* to be the most important allergic excitant such as in peripheral vascular disease certain cardiac arrhythmias tobacco angina angina pectoris and especially in younger persons complete cessation of smoking is imperative Two categories of individuals may be chiefly affected by tobacco allergy those who are constitutionally allergic and those who may become so as a result of excessive smoking

The clinical course in patients who refuse to stop smoking is chronic progressive cardiovascular disease This may be characterized in some cases by arteriosclerosis superimposed on allergic inflammatory vascular lesions as exemplified in cases with thromboangiitis obliterans Persons who do not show any symptoms from smoking may smoke in moderation

PART II DELAYED REACTIONS

In contrast to the acute reversible cardiovascular symptoms resulting from allergy to various exogenous substances are the delayed reactions in the cardiovascular system caused by polyvalent sensitization to intrinsic as well as extrinsic agents such as bacteria and drugs especially penicillin and sulfonamides

Pathophysiology The delayed forms of hypersensitivity are manifested by fibrinoid degeneration of collagen in the connective tissue and blood vessels eosinophilia leukocytic infiltration of the walls of blood vessels swelling and degeneration of endothelium thrombosis and necrosis followed by scar formation These changes may be elicited in the myocardium heart valves arteries veins lymphatic tissue etc in the systemically sensitized rabbit[8]

Patients who become sensitized may similarly develop various degrees of hyperergic vascular disease Those who succumb despite all forms of treatment reveal the following anatomic alterations

Autopsy shows widespread vascular changes characterized by various degrees of necrotizing arteritis fibrosing arteritis in long standing cases inflammatory changes in the veins and granulomatous lesions within the vessel walls and in the connective tissue of the lungs and other organs in the body The lesions in the heart responsible for the abnormal electrocardiographic changes vary in different cases In some they consist of diffuse eosinophilic infiltration of the myocardium (so-called eosinophilic myocarditis) in others there is fibrosis of the myocardium with minimum involvement of the coronary vessels while in still others varying degrees of arteritis in the coronary vessels including periarteritis nodosa are seen Granulomatous nodules simulating the Aschoff body have also been seen occasionally in the connective tissue septums of the myocardium (see also Chap 10)

Clinical Manifestations The character of the presenting symptoms depends on the type and number of organs affected in the allergic response Patients in whom the connective tissue vascular structures of the lung are the primary points of antigenic impact develop symptoms of bronchial asthma or cough which are superficially indistinguishable from those in the ordinary cases of asthma The difference between the two however is not so much in the exciting agents as in the character of the basic tissues affected in the allergic response In the ordinary asthmatic patient the allergic reaction occurs primarily in the ectodermal structures of the bronchi and in contiguous elements such as capillaries glands and musculature In such patients roentgenograms of the lungs are negative The eosino

phil count averages about 10 per cent The heart is usually normal but may become involved secondarily in the form of cor pulmonale in those individuals who develop chronic emphysema with pulmonary insufficiency

Asthmatic patients whose symptoms are associated with reactions in *the connective vascular tissues in the lung may manifest* migratory eosinophilic infiltrations in various lobes of the lungs together with cough and wheezing respirations fever ranging from 99 to 104 F and marked eosinophilia This eosinophilia distinguishes asthma caused by vascular allergy from the ordinary cases of bronchial asthma it may vary from 20 to 80 per cent with a total white blood cell count from 8 000 to 50 000 or higher The underlying pulmonary lesions are usually not detected on physical examination but are readily demonstrable roentgenographically They appear as miliary infiltrations or soft exudative pneumonic patches Both types may be reversible Simultaneously with the pulmonary lesions there may be an extension of the hyperergic vascular process to other organs such as the heart serous membranes kidney liver as well as nervous and cutaneous structures giving rise to the picture of generalized vascular disease i e periarteritis nodosa Eighteen per cent of patients with periarteritis nodosa have asthma as their major presenting symptom Other patients in this category who do not develop this widespread vascular disorder but who show reactions limited to two or three organs may therefore be regarded as *formes fruste* of hyperergic vascular disease On the basis of such variations in tissue response in a study of 21 cases reported by Harkavy it was possible to classify the various manifestations into the following clinical syndromes

1 Bronchial asthma and cough with recurrent pulmonary eosinophilic infiltration (Loeffler type) reversible

2 Recurrent attacks of bronchial asthma or cough with prolonged pulmonary eosinophilic infiltrations accompanied by electrocardiographic changes indicative of myocardial involvement reversible in the early stages

3 Recurrent attacks of bronchial asthma associated with

a Electrocardiographic abnormalities characterized by alternations in the deflections and amplitudes of the P waves and QRS complexes

b Electrocardiographic abnormalities plus eosinophilic exudations in (1) pleura and pericardium (reversible) and (2) pleura pericardium and peritoneum giving rise to Pick s syndrome (may or may not be reversible)

c Involvement of the kidneys liver and gastrointestinal tract

d Reactions in the skin such as urticaria angioneurotic edema purpura and subcutaneous nodules suggestive of periarteritis nodosa

Course and Treatment *The clinical course in these cases depends* on the cause and the extent of involvement In cases of pulmonary eosinophilia caused by food allergy or parasitic infestation (*Ascaris*) elimination of the incriminating food or parasite by chemotherapy causes resolution of the process In cases where acute infections or drugs are responsible for the pulmonary lesions the condition may subside spontaneously or with treatment by means of hormones such as ACTH and cortisone In more chronic cases caused by focal infections where not only the lungs but also the heart pleura and other tissues are involved therapy consists of eradication of infected foci especially those in the sinuses and temporary use of antibiotics where indicated supplemented by ACTH or cortisone prednisone etc These hormones are most important Immunization with specific allergens to prevent recurrences may also occasionally have to be carried out The prognosis in these cases is usually good In instances of vascular allergy caused by drugs such as penicillin or sulfonamide discontinuance of the drug is imperative In addition treatment with ACTH or a corticosteroid should be instituted as soon as possible In cases where the hyperergic vascular disease becomes generalized and the picture of panarteritis supervenes the sooner treatment with ACTH or a corticosteroid is started the better Once this disease has progressed the period of survival depends on the degree of cardiac or renal involvement Where the heart and kidney are not affected the patient has an excellent chance of recovery In cases where they are involved the period of survival varies from one to four years

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Moses L Furman

HEMATOLOGIC ALLERGY

For a long time allergic reactions and diseases have been known to involve the blood in one way or another Eosinophilia for example has been intimately associated with allergy Diminished coagulability and neutropenia are changes that occur in anaphylaxis Symptomatic purpura can result from an allergic involvement of blood capillaries producing an increased permeability with extrusion of blood cells However all these hematologic effects and in some instances actual blood loss are regarded as secondary in nature either resulting from a local allergic reaction elsewhere in the body or simply occurring as part of a systemic allergic reaction

There are however certain phenomena also based on an antigen antibody reaction which can directly and primarily affect and destroy red blood cells white blood cells or platelets The antibodies in this case are either natural isoantibodies or acquired autoantibodies capable of reacting adversely to one of the blood elements In other words the body naturally possesses or has the ability to produce *antibodies inimical to its own tissues including the blood cells*

This of course appears paradoxic since antibodies are actually immune bodies ordinarily regarded as protective substances capable of preventing or checking disease Nature apparently intended that antibodies should neutralize or at least render harmless foreign or offending substances introduced into the body and thereby maintain normal homeostasis

However there are certain antibodies which are potentially dangerous to the body because by their ability to unite with their spe

cific antigens they actually can produce untoward effects and even disease This phenomenon is the *sine qua non* of allergy A well known example of this type of reaction is hay fever or pollinosis in which the symptoms result from the union of pollen antigen and its specific antibody or reagin found in the blood of certain individuals Furthermore there is abundant experimental proof in animals [1-4] and some evidence in human beings [7] that autoantibodies can be produced to one s own kidneys heart brain and skin (see Chap 6) The reaction these produce in the specific organ or tissue is also regarded as an allergic phenomenon or disease

In the same manner blood elements can be injured or destroyed on an allergic basis However although hematologists recognize this mechanism they have not been classifying such diseases under the specific heading of allergy An examination of general hematologic classifications in various texts reveals the discrepancies and at times confusion that exist among hematologic categories of certain acquired hemolytic anemias agranulocytoses and thrombocytopenic purpuras due to isoantibodies or autoantibodies For example a distinction is made between *immunologic* and *allergic* agents [8] and such general terms as *immunohemolysins* [9] are employed when describing the allergic blood diseases Whitby and Britton [10] classify *allergic hemolytic anemias* under the heading Infective Toxic or Poisonous Factors In his excellent book on hematology under Transfusion Reactions Sturgis [11] lists as allergic only those reactions resulting in asthma urticaria or the other familiar symptoms of allergy Peculiarly enough however hematologists recognize the existence of blood allergy in which none of these time honored allergic symptoms is present The terms *drug sensitivity* and *drug allergy* are very commonly used in hematology

Since the following blood conditions stem from or are strongly suspected of being the result of reactions implicating isoantibodies or autoantibodies one seems justified in listing them under the broad heading of allergy In the author s opinion this would serve to simplify their classification and also to emphasize the mechanism involved

Allergic conditions affecting red cells—Certain Acquired Hematologic Anemias

A Primary
- 1 Based on a so called normal or physiologic mechanism
  - *a* Transfusion reactions due to incompatible main blood groups
- 2 Based on an abnormal or pathologic mechanism
  - *a* Transfusion reactions due to incompatible Rh factors
  - *b* Erythroblastosis fetalis

c Paroxysmal cold hemoglobinuria
d Favism
e Drug reactions (?)
f Idiopathic (unknown etiology but with demonstrable autoantibodies to red cells)

B Secondary (in which the primary disease is not allergic but demonstrable autoantibodies to red cells are present) chronic lymphatic leukemia lymphosarcoma carcinomatosis Boeck s sarcoid tuberculosis lupus erythematosus

Allergic conditions affecting white cells—Certain Agranulocytoses

A Drugs aminopyrine thiouracil phenylbutazone procaine amide dinitrophenol antihistamines chlorpromazine sulfapyridine chloramphenicol streptomycin Diamox (acetazoleamide)

B Idiopathic (unknown etiology but with demonstrable autoantibodies to white cells)

Allergic conditions affecting platelets—Certain Thrombocytopenic Purpuras

A Drugs Sedormid quinidine

B Idiopathic (unknown etiology but with demonstrable autoantibodies to platelets)

The division into so called normal or physiologic and abnormal or pathologic anemias has its analog in the classification of the more familiar and generally accepted allergic diseases Normal or physiologic allergy is represented by conditions such as serum sickness which the *majority* of people allergic or nonallergic develop when injected with an adequate amount of foreign serum and contact dermatitis especially that due to ivy primula certain dyes and vegetable oils demonstrated after adequate exposure to these substances These are practically universal reactions On the other hand only a small *minority* or about 10 per cent of all human beings develop the abnormal or pathologic forms of allergy such as asthma hay fever or atopic eczema

Normal or *physiologic* anemia is so termed because most people manifest it when transfused with blood which is incompatible with their own blood groups The antibodies involved are natural isoagglutinins which are universally present in all human beings As is well known this type of reaction results in the injury and destruction of the recipient s own erythrocytes

We are fully aware of the inadequacy of the appellation normal or physiologic anemia However until a better term is offered these will serve as an initial working basis

In the less common abnormal or pathologic anemias there is another type of transfusion reaction which involves the Rh factors In

this case the antibodies are acquired autoagglutinins of which there are a great variety Erythroblastosis fetalis which is also due to the action of the acquired anti Rh agglutinins occurs in Rh positive in fants born to Rh negative mothers who have been sensitized to Rh positive blood by previous pregnancies or by transfusions with in compatible Rh positive blood The hemoglobinurias both syphilitic and nonsyphilitic are caused by so called cold autoantibodies the syphilitic form being caused by a hemolysin the nonsyphilitic by an agglutinin

Favism is a disease which results from the ingestion of the fava bean which as the antigen reacts with its specific autoantibody probably a hemolysin producing hemoglobinuria anemia and jaundice This antibody is a skin sensitizing antibody and there fore can be demonstrated by the ordinary skin test This disease is probably the closest link between the allergic hematologic disorders and the more familiar allergies such as hay fever where the antibody can also be detected by the simple skin test

Many primary idiopathic and secondary acquired hemolytic ane mias belong to the allergic group The mechanism here is thought to be an adhesive coating of the erythrocytes by an abnormal globu lin which is the autoantibody It is probably derived from the lymphoreticular system and renders the red cells susceptible to ag glutination and hemolysis Hemolytic anemia and jaundice due to other foods have recently been described in allergic patients by Barr and associates [1]

This erythrocyte bound antibody globulin may be detected by the Coombs test [13] which is based on the agglutination of red cells by the reaction between the erythrocyte bound antibody globulin and anti human globulin antibody prepared from rabbits immunized with normal human serum or globulin Other investigators [14] have indicated that favism and hemolytic reactions to drugs result from low activity of glucose 6 phosphate dehydrogenase and low rate of incorporation of radioactive glycine into glutathione Genetic stud ies suggest that this abnormality is hereditary and sex linked

Regarding the allergic agranulocytoses and thrombocytopenic purpuras it has been known for many years that certain drugs notably aminopyrine are capable of producing neutropenia and agranulocytosis in certain individuals [15] The mechanism by which aminopyrine causes agranulocytosis has long been regarded as al lergic since the ingestion of very small amounts of the drug pro duces these symptoms Dameshek and Colmes [16] found that patients who have recovered from aminopyrine agranulocytosis developed extreme granulocytopenia when a few milligrams of the drug were

injected intradermally These investigators also produced local wheal and flare reactions with rapid leukopenia in such individuals by the intradermal injection of a mixture of aminopyrine and blood serum The nature of this sensitization has not been explained and attempts to demonstrate a definite immunologic mechanism have been unsuccessful for the most part

Recently however European workers demonstrated the presence of leukoagglutinins in many such cases Moeschlin and Wagner[17] produced leukopenia in two normal persons within twenty to forty minutes after transfusion of blood from an aminopyrine sensitive patient The serum of this patient also was capable of in vitro agglutination of autologous and homologous leukocytes In this country Schwartz and Hass[18] found leukoagglutinins in a case of idiopathic agranulocytosis

Sedormid[19] and quinidine[20] are capable of producing in some individuals a platelet agglutinin which can destroy circulating blood platelets and megakaryocytes in the marrow with resultant thrombopenic purpura

Harrington *et al*[21] demonstrated conclusively the existence of a thrombocytopenic factor They transfused whole blood or its plasma equivalent from patients with thrombocytopenic purpura to normal individuals and produced a prompt often dramatic drop in their blood platelets This decrease persisted for four to seven days There was suggestive evidence that this factor is present in the globulin fraction of plasma It did not disappear after splenectomy but did disappear after cortisone administration

Recent studies by Stefanini and Damashek with quinidine thrombopenia indicate that quinidine may attach itself more or less firmly to the platelet which may thus become modified and act as an autoantigen A highly specialized autoantibody develops which reacts with platelets only in the presence of quinidine Apparently quinidine acts as a hapten which becomes fully antigenic in the presence of platelets

PROPHYLAXIS

It is obvious that in the present state of our knowledge prophylaxis is not always possible especially for idiopathic and secondary blood disorders However prophylaxis is feasible when contemplating a transfusion In addition to the usual matching and cross matching of the bloods it is essential to determine the Rh factors This should be done particularly when the patient is an Rh negative pregnant woman Such a patient should be scrupulously observed

for the development of anti Rh antibodies if they are present proper measures should be taken immediately to save the fetus which is Rh positive Such measures would include induction of labor or even Cesarean section

Prophylaxis is also possible in the larger group of drug allergies involving especially the white cells and platelets Antibiotics and chemotherapeutic agents should be prescribed only when there are definite and urgent indications that they are needed The physician must always remember the possible dangers involved in their use and his responsibility when prescribing or administering them Patients receiving these drugs should be observed for urticaria or other skin reactions fever joint pains or swellings and gastrointestinal symptoms When such treatment is continued for some time the blood should be examined at regular intervals particularly for evidence of eosinophilia and leukopenia

When new drugs are tried it might be well to examine the structural formula Drugs containing benzene rings to which are attached N NH or NH groups are especially dangerous to some people Recognition of this possible hazard will lead to increased vigilance since there is no simple reliable test for sensitivity to a given drug

TREATMENT

Any drug causing a blood disorder should of course be promptly discontinued as should any harmful food such as the fava bean

In the newborn with erythroblastosis exchange transfusions are indicated In idiopathic thrombocytopenia and in idiopathic anemias splenectomy often checks the disease by removing a primary site of blood destruction or antigen production and at the same time eliminates a site of harmful autoantibody formation

Antihistamines have been ineffectual in hematologic allergy since histamine apparently plays a minor role at most

In unmanageable or progressive granulocytopenia penicillin and other antibiotics in large doses should be administered to control infection

The most promising of the more recent therapeutic agents are the cortisone derivatives and ACTH They are particularly valuable in the hemolytic anemias and in thrombocytopenia in which they have proved capable of controlling the disease until the cause has been determined and eliminated The precise mechanism of this steroid action is not known but it is suspected to involve some interference with the harmful immune responses

Since drugs are so vitally important as etiologic agents in hematologic allergy it might be well to remember Damashek s six commandments

1 Do not use drugs unless it is essential

2 Do not use potentially toxic drugs unless the need is impelling

3 If a finger of suspicion is pointed at a drug avoid it

4 Investigate the formula

5 Be alert for side effects such as fever joint pains skin eruptions and the like

6 Do not rush into powerful and possibly harmful therapy for in treatment conservatism is a commendable virtue

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GASTROINTESTINAL ALLERGY

With a broadening concept of allergy, it has become apparent that all the tissues of the body are capable of taking part in the allergic reaction. It is not unexpected, therefore, that allergic reactivity finds a target area in the gastrointestinal tract.

Gastrointestinal allergy implies the affection of all or any part of the gastrointestinal tract by foods, occasionally by drugs, or rarely by inhalants. Although foods are the most frequent provocative agents, the term *food allergy* is not synonymous with *gastrointestinal allergy*. Food allergy implies hypersensitiveness to foods regardless of the shock organ involved and does not have specific reference to the gastrointestinal tract (see Chap. 42). Further confusion results from the erroneous use of the term gastrointestinal allergy to cover many obscure digestive ailments, some of which may be expressions of other disease processes, e.g., infectious, degenerative, or psychic.

Sensitivity to food is most frequently encountered in infancy and childhood and usually decreases gradually and spontaneously with maturity. Consequently the more classic expressions of gastrointestinal allergy are to be found in early childhood. The decrease follows no exact age pattern. Specific gastrointestinal sensitivity is of short duration with most individuals but lifelong with some.

Because of the confusion with food allergy, the indiscriminate use of the term *allergy* in diagnosis, and the lack of a pattern of sensitivity, it is difficult to compile statistics on the incidence of gastrointestinal allergy.

Since drugs are so vitally important as etiologic agents in hematologic allergy it might be well to remember Damashek s six commandments

1 Do not use drugs unless it is essential

2 Do not use potentially toxic drugs unless the need is impelling

3 If a finger of suspicion is pointed at a drug avoid it

4 Investigate the formula

5 Be alert for side effects such as fever joint pains skin eruptions and the like

6 Do not rush into powerful and possibly harmful therapy for in treatment conservatism is a commendable virtue

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Symptoms may group themselves into patterns or syndromes not commonly characteristic of disorders on a hypersensitive basis. Among those now recognized as being provoked on occasion by an allergic reaction are recurrent vomiting[8] pylorospasm[7] the celiac syndrome[10] regional enteritis[11, 12] and mucous or ulcerative colitis[12]

DIAGNOSIS

The varied symptomatology resulting from gastrointestinal allergy makes it necessary that organic disease and psychic causes be ruled out before considering hypersensitiveness. In my opinion allergy accounts for only a small percentage of the digestive disorders encountered in adults or even in children.

A careful history may possibly elicit an association between ingestant and symptoms; it identifies the atopic individual and it may indicate significant food dislikes or show that commonly allergenic foods are being eaten in large amounts and are therefore suspect.

Unfortunately cutaneous tests which are frequently diagnostic in other expressions of allergy are of limited value here. Occasionally however cutaneous reactions of the immediate wheal type are obtained with offending antigens. Subjects experiencing immediate pronounced gastrointestinal disturbances are the ones most frequently giving marked dermal reactions[13]

A detailed food diary recording daily intake of all possible ingestants including vitamins, medications and between meal snacks, the quantity ingested and time relationship to the occurrence of symptoms can be most helpful.

Allergic reactions in the gut are characterized pathologically by mucosal edema, hyperemia, hyperactivity of the secretory glands and secondary muscle spasm. These findings have been substantiated in experimental studies on the exposed digestive tracts of passively sensitized Rhesus monkeys and of human beings[14, 15]

Trial ingestion of suspected foods incriminated by the history or by the food diary should be undertaken, testing only one food at a time. Production of symptoms simulating the clinical pattern on repeated trials is a most important method of establishing etiology.

It might be pointed out however that the production of symptoms with trial ingestion of a food and elimination of symptoms with its avoidance do not necessarily imply an allergic mechanism. Disturbances regularly following ingestion of certain foods or drugs may indicate the causative substance but do not establish its allergenicity. Such disturbances may be due to physical, chemical or

COMMENT

Nutritional impairment of children with chronic allergic gastrointestinal reactions as of those with other alimentary disturbances is to be expected There must certainly be incomplete utilization of nutrients and vitamins resulting from disturbed motor function In addition local angioedema may affect the permeability of the gut for the ready passage of nutrients Clinically in severe instances one sees skin lesions which are highly suggestive of vitamin A deficiencies and evidences of other vitamin deprivations Growth is sometimes stunted and there may be impairment of musculature In support of this in studies as yet incomplete I have observed interference with the utilization of vitamin A as indicated by an abnormally low absorption curve in a few children with severe gastrointestinal allergy

It has been hypothesized that allergic hyperactivity of the human stomach and intestines may result in a *locus minoris resistentiae* with resultant tissue damage This offers an additional consideration in the causation of gastric and duodenal ulcers and ulcerative colitis [1] -[4] Should future studies confirm this theory many foods may be incriminated which now are considered innocuous and are routinely used in the ulcer diet

Henoch s purpura and migraine [5] are now recognized as being allergic reactions on occasion The gastrointestinal components of these syndromes have a pathologic physiology which may differ from that characteristic of the better known allergies

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42 | *Harry Markow*

FOOD ALLERGY

During the period in which allergy was emerging as a specialty from the realm of internal medicine, food allergy was associated with that group of gastrointestinal disorders which occurred in sensitive individuals following the ingestion of certain foods. Now, however, it is recognized that the ingestion of foods to which the patient is sensitive may produce a variety of functional disorders, including asthma, allergic rhinitis, urticaria, angioedema, eczema, migraine, gastrointestinal disorders, and other bizarre syndromes which are difficult to diagnose and which do not fit into the various disease categories. Any food may be the culprit and may be responsible for a single allergic manifestation or a combination of them.

While food allergy is considered relatively uncommon as compared to inhalant allergy, it is possible that more intensive studies of the relation of foods to symptoms in allergic patients will bring increased recognition of its incidence. There is often a tendency to rely solely on the results of skin tests for the determination of the etiologic agent or agents in allergy. Slight skin reactions to foods are often overlooked or ignored. Tuft[1] has justly claimed that since slight reactions to inhalants are not ignored, slight reactions to foods should not be ignored. However, this is not generally practiced. Another reason why food skin tests are held in low esteem is the fact that many positive reactions with foods cannot be confirmed by clinical trial. On the other hand, there are cases in which foods may cause symptoms, yet the skin tests with these foods are negative. These difficulties have led many allergists to disregard the results

of skin tests with foods and some have discontinued skin testing with foods entirely depending rather on clinical trial and error diets elimination diets or intentional feeding diets

In a previous study it was shown that by the intentional feeding test only 4 5 per cent of positive food skin tests in older children and adults were of clinical significance It may be argued that this finding invalidates the food skin test as a reliable diagnostic procedure However food allergy occurs in a limited number of allergic patients and in those cases in which food skin tests prove to be of clinical significance the positive tests are of importance in the etiologic diagnosis It is also a fact that many positive food reactions that cannot be confirmed clinically represent past sensitivities which have been outgrown clinically without loss of the cutaneous sensitivity The accuracy of the food skin test is evidenced by the finding[2] that the negative test was confirmed clinically in 98 2 per cent of the clinical trials Hence food skin tests although clinically significant in only a limited number of patients are a reliable diagnostic procedure for that group Clinical trial with foods to which a patient has a positive skin reaction is often rendered difficult because the tests are made with foods extracted in the raw state but eaten in the cooked state and it has been shown[3, 4] that the cooking of some foods may denature them to the extent that they may be tolerated in limited amounts even by individuals sensitive to them

Tuft found that the incidence of positive skin test reactions to commonly eaten foods is definitely and significantly higher in the allergic than in a control group whereas with foods uncommonly eaten the difference is not statistically significant He maintained that skin tests with commonly eaten foods are of value and should not be omitted from routine skin tests From my clinical observation skin tests with food allergens are of value in the study of all allergic patients but the clinical study of the etiologic factors must not end with mere skin testing but must continue as long as the patient is under observation

It is generally agreed that food allergy is more common in infants and young children In adults foods alone are rarely the cause of allergic manifestations The reason foods are often the sole cause of symptoms in infants is not clear As the child grows older and comes in contact with more environmental allergens there is a tendency to acquire sensitivities to inhalants At the same time clinical sensitivity to foods tends to disappear often spontaneously without the loss of the cutaneous sensitivity in many such cases Hence in older individuals the presence of positive skin tests with food allergens may represent a past rather than a present sensitization (see Chap

55) That is one reason why positive food tests in older patients often cannot be confirmed clinically even in the presence of marked skin reactions Since the growing child acquires inhalant sensitivities which tend to remain throughout adult life these reactions to inhalants in adults are frequent and important clinically However attempts at clinical trials with foods in the presence of inhalant allergies will not give satisfactory results especially if the clinical trials are made during pollen seasons in the presence of pollen sensitivity or if the inhalant sensitivities are not controlled

The diagnosis of food allergy is not the simple procedure of skin testing with a great many food extracts and the mere elimination of foods to which there is a positive reaction Such a procedure if carried to the extreme will result in a monotonous and restrictive diet and in vitamin and mineral deficiencies A thorough and complete history must first be recorded beginning from infancy and extending to the onset of the present illness A family history as well as a past personal history of allergic disorders will give support to the possibility that allergy is involved in the present illness A blood eosinophilia will also give weight to such a possibility

The diet of the patient should be adequately studied especially for a history of likes and dislikes In cases where symptoms develop rapidly after a meal the causative food is not difficult to spot Where the symptoms develop hours after a meal especially with other meals intervening the problem is difficult to analyze In immediate clinical reactions following the ingestion of foods one can expect a positive skin test to the offending food In delayed clinical reactions skin tests with foods are usually negative and tests are of little value in determining the offending food Here elimination diets or intentional feeding diets are the method of choice to track down the offender The main difficulty arises when the offending food is milk egg or wheat each of which is a common ingredient of many other foods so that its presence is not generally suspected by the patient It is incumbent on the patient to study and know the ingredients of all foods which he consumes so that if sensitive he will be better able to avoid any or all of these three foods in the diet

My favorite method of detecting food offenders is to instruct the patient to note on paper all foods eaten at each meal with a statement after each meal as to whether or not any symptoms developed Such a statement should also be made for any symptoms arising between the early morning hours and breakfast since such symptoms may be traced to the dinner or after dinner snacks of the previous day By studying these reports daily for two to three weeks one can often detect the onset of symptoms after a new food or after the

repeated use of a certain food The elimination of these foods from the diet should result in an asymptomatic state and the intentional ingestion should be followed by symptoms These trials however should be repeated at least three times before any conclusion is reached in order to avoid error in attributing the relief of symptoms or incitement of symptoms to the manipulation of that food Inhalant allergy or psychosomatic factors may be the reason for either the symptoms or the relief of symptoms after a single trial

Another method for incriminating foods is to allot to the patient a diversified list of 24 foods to which he failed to react on skin testing If there is no improvement in symptoms on this diet after a trial period of two weeks four foods (one vegetable one fruit one cereal and one meat) are eliminated every two weeks from the diet If the symptoms are unchanged after the elimination of each of the 24 foods and if the report of the patient is reliable the conclusion may be drawn that foods do not play an important role in the case While food trials are being studied it is essential that all other therapy remain unchanged On many occasions however the patient s dietetic report may be unreliable the mother insisting that the child did not eat chocolate and the child reminding the mother of the time that she allowed him to eat a tiny piece of chocolate

Some remarks regarding skin testing with food allergens are in order in any discussion on food allergy (see Chap 12) Skin tests are not a laboratory procedure Patients should not be referred to a laboratory to be tested for allergy Only the experienced physician who has taken a complete history and has examined the patient is in a position to interpret the results of skin tests in the proper perspective Skin tests with foods are notoriously changeable from time to time and I believe that the diet of the patient plays a part in this Many foods give marked reactions which cannot be confirmed by passive transfer or by clinical trial Occasionally a food will give a positive clinical test in the absence of a positive skin test Certain food extracts give positive reactions in a high percentage of patients tested in reality these are irritative reactions and should be ignored unless confirmed by positive clinical test Such irritative reactions are common with banana tea sweet potato spinach and a few other foods It is essential that food extracts be replenished at regular intervals since there is a tendency for many such extracts to deteriorate with time becoming cloudy and precipitated Care should be exercised in buying extracts for testing for the extracts must be stable and the source reliable In testing with foods it must be remembered that certain foods will give marked and often severe constitutional reactions This is more common among the fish and

nut extracts but there are some extremely sensitive individuals who will give similar severe reactions to milk eggs and seeds such as mustard It is best to try to obtain a history of clinical sensitivities before testing since most patients are aware of specific foods which give them severe reactions A positive skin test with a food allergen may be of academic interest only however a positive skin test associated with a history of the development of symptoms after the ingestion of this food may be regarded as evidence of causal relationship especially if the occurrence of symptoms can be repeatedly demonstrated A food that causes symptoms on one occasion but not on other occasions should not be considered a truly causative factor unless eventually confirmed by repeated trials there may be a quantitative as well as a qualitative factor in the sensitization Symptoms due to the ingestion of food should be relieved by the avoidance of that food and the repeated clinical demonstration of this food symptom relationship is ample evidence of cause and effect If this causal relationship is associated also with a positive skin test that is added evidence that the specific food is a cause of symptoms and should be eliminated from the diet

Results in the treatment of food allergy will depend entirely on success in ferreting out the offending food or foods Once this is accomplished the next step is the complete elimination of offending foods from the diet with proper substitution of other foods to maintain nutrition and to avoid monotony in feeding In infants milk is the important factor in the diet Proper substitution is often difficult Modification is possible in some cases Where sensitivity is to the whey fraction human goat or boiled milk may be substituted Where the casein fraction is involved soybean milk may be used Soybean milk has been used successfully as a substitute for mammalian milk in cases of allergy due to cow s milk Homogenized meat milks made up of individual types of meat have been used where other types of milk failed to give relief of symptoms In adults milk sensitivity is often of only moderate degree and well cooked milk is tolerated without difficulty While milk is used in the preparation of many foods it is the opinion of many that one does not have to go beyond the mere elimination of whole milk to maintain tolerance in the average case Similarly eggs and wheat are used extensively in the preparation of many food products and the ingestion of these should be watched for and avoided (see Chap 13) Desensitization to foods is seldom resorted to

Where food allergy is suspected and the cause of the food allergy has not been determined by history or skin tests extensive trials with elimination diets intentional feeding diets and other estab

lished diets should be tried It is a long tedious procedure but if the patient will cooperate and if the inhalants can be ruled out as a cause of symptoms the ultimate success in the treatment of food allergy will be greatly appreciated by the cooperative patient and the painstaking allergist

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43 | *David Merksamer*

ALLERGY TO MOLDS

The spores of saprophytic fungi originating from growing and dead vegetation and from the soil are frequently responsible for allergic respiratory conditions Because of their light weight and minute size these spores are readily wind borne and widely disseminated and under proper conditions germinate to form new colonies of fungi or molds When they are present in the atmosphere in significant quantities they may produce allergic symptoms similar to those caused by pollen

Allergy to molds is not a new concept[1 1] However the condition was formerly believed to be relatively uncommon and to affect only those individuals whose occupations exposed them to large numbers of mold spores as for example farmers and mill workers It was also generally believed that atmospheric mold spores were primarily of significance in the agricultural Midwestern states and were not present in the East in sufficient quantities to cause allergic symptoms[13, 14] In the New York metropolitan area the importance of mold spores as atmospheric allergens was not appreciated until 1948 when the extensive pollen surveys carried on at the Allergy Laboratory of the Jewish Hospital of Brooklyn[1] afforded the author an opportunity to study the mold spore content of the air at many localities in that area As a result of these studies it was established that the New York metropolitan area has a definite mold season which is significant clinically It begins about the middle of June and lasts until the end of October or the middle of November[16] A similar pattern prevails throughout the country with variations

in the mold counts dependent upon the humidity temperature and flora available as a host for the saprophytic molds (Fig 43 1) (See Appendix II)

The spores found in largest quantities on the slides are those of *Alternaria* and *Hormodendrum* Spores of *Helminthosporium, Acrothecium* smuts and rusts are also seen Among all these *Alternaria* is the most important from a clinical point of view The greatest numbers of these spores are usually found in the atmosphere in July and again in September or October (see Fig 43 2)

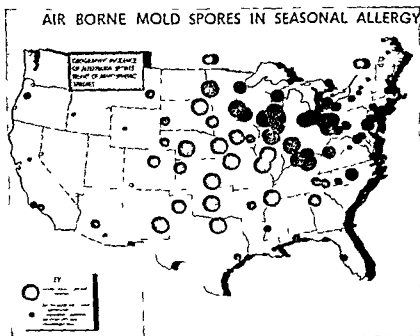


Fig 43 1 Map showing distribution and concentration of mold spores in various sections of the United States Large discs denote places of greatest air contamination small discs denote places of minimum contamination Comparative concentrations are shown with discs of intermediate sizes

The spores of *Aspergillus Penicillium Mucor Rhizopus Phoma* yeasts and other molds can be identified only on culture plates These spores have no seasonal incidence They tend to be of greater significance in indoor than in outdoor exposure [17, 18]

Among wind borne allergens mold spores are second in importance only to pollens While a small percentage of mold sensitive patients are sensitive to molds alone most are allergic to other allergens as well especially to pollens More are sensitive to ragweed than to grass or tree pollens [19] All hay fever patients should be ro

tinely tested with mold extracts and careful histories should be taken as to the exact dates of symptoms The existence of mold sensitivity is highly important in treatment since failure to take this factor into account is often responsible for poor clinical results with pollen therapy It must be remembered that the incidence and importance of mold allergy vary materially in different sections of the country In the Middle West for instance the concentration of atmospheric mold spores is much higher than in the Atlantic and Pacific coastal states [13, 14]

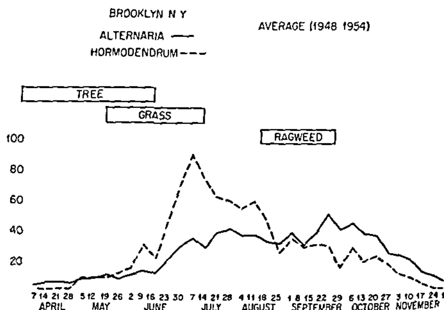


Fig 43 2 Averages of the seasonal occurrence of *Alternaria* and *Hormodendrum* in New York City (Brooklyn) during the seven year period from 1948 to 1954 inclusive The chronological relationship of the mold season to the pollinating periods for trees grasses and ragweed is also presented The counts are expressed in terms of number of spores per square centimeter of exposed slides

In the majority of cases of mold allergy the symptoms begin early in life usually in the first or second decade Most cases of mold sensitivity seen by the author have been in children The explanation for this is not yet apparent

Among mold sensitive patients bronchial asthma is most frequently the predominating symptom occurring either alone or in association with rhinitis however rhinitis also is often seen alone The asthmatic symptoms usually are ushered in by a dry nonproduc

tive cough which is worse at night and which is followed later by the characteristic episodes of dyspnea and wheezing As a rule ophthalmic symptoms are not present In pollinosis on the other hand nasal and eye symptoms rather than asthma are the most common manifestations The diagnosis of mold sensitivity can be made in a large percentage of cases from the history Summer rhinitis or asthma in a patient who either does not react by skin tests to pollen or whose symptoms are not seasonal in accord with positive pollen reactions is suggestive of mold sensitivity Frequently mold symptoms begin between the grass and ragweed pollinating seasons and continue long after ragweed pollination has ceased (See Fig 43 2) These patients often give a history of symptoms which last until frost Attacks occurring in musty rooms in damp basements or in barns are also suggestive of mold sensitivity

Perennial symptoms due to molds are considerably less common than seasonal symptoms As a rule the perennial symptoms occur in individuals exposed to large numbers of molds in their homes or in their occupations Occupational exposures are encountered among furniture repairers who work with old bedding and overstuffed furniture gardeners fruit and vegetable workers farmers or botanists who work with vegetation mill workers who are exposed to molds in grain and mill dust and others who work in damp or musty places *Aspergillus* and *Penicillium* which have no definite seasonal prevalence are usually the offenders in patients with perennial symptoms *Alternaria* rarely causes perennial symptoms

A small percentage of patients with eczema who have exacerbations of their skin lesions during the summer and fall months show positive skin tests with mold extracts and the clinical course can be correlated with the mold spore content of the air The correlation of symptoms with the atmospheric mold spore content the positive skin tests the ease with which acute flare ups can be produced by an overdose of subcutaneously administered mold extracts or by clinical exposure of the patient to mold spores by inhalation and the improvement produced in some cases by specific hyposensitization seem to indicate that molds are an important etiologic factor in this type of case [9, 1]

Skin tests with mold extracts performed preferably by the intracutaneous technic elicit immediate whealing reactions which are important in the diagnosis of mold allergy However the most important aids in the clinical and differential diagnosis in mold sensitive cases are daily mold spore and pollen counts with which symptoms may be correlated

Skin testing with mold extracts requires the same precautions that

are taken in testing with pollen extracts Not more than 0 01 to 0 02 ml of a 1 10 000 dilution of any mold extract should be injected intracutaneously as an initial test If after eight to ten minutes the reactions are negative or slight a 1 1 000 dilution may be tried Finally a 1 100 dilution may be used Because constitutional re actions often occur from skin tests with mold extracts especially with *Alternaria* few tests should be done at one time

Hyposensitization therapy with mold extracts consists of sub cutaneous injections administered once or twice weekly prior to the season The schedule depends on when the patient is first seen and the expected date of symptoms The size of the initial dose is based on the degree of skin sensitivity of the patient as determined by tests with serial dilutions of the mold extracts The usual starting dose is 0 1 to 0 3 ml of a 1 100 000 or 1 10 000 dilution Doses are in creased by approximately 50 to 100 per cent increments in the weaker concentrations and by smaller increments with the more concentrated extracts The usual maximal dose is 0 1 to 0 5 ml of a 1 100 dilution However there are many patients who because of their extreme sensitivity cannot tolerate such a dosage schedule In these cases smaller initial doses and smaller increments are ad visable During the season the dosage should be reduced After a course of preseasonal treatment which has been well tolerated and has proved effective perennial therapy may be instituted

Rigid precautions should be taken with mold extract therapy Con stitutional reactions occur frequently because these patients as a group have a lower tolerance for mold than for pollen dosage The constitutional reactions occur most frequently in children and pro duce symptoms generally limited to the nasal and bronchial mucous membranes This is in contrast to the constitutional reactions oc curring with pollen therapy which are unusual in children and are characterized by urticaria as an initial and predominating symptom

Approximately 80 to 90 per cent of mold sensitive patients ob tain satisfactory relief from hyposensitization with the proper mold extracts The fact that so many mold sensitive patients are also troubled by pollen makes the management of these cases more dif ficult The results in these cases however are generally most gratify ing The importance of mold sensitivity as a factor to be reckoned with in the management of previously unsolved cases of summer respiratory allergies has definitely been established

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44 | *S Senior Sack*

PHYSICAL ALLERGY

On the basis of a careful study of 37 cases selected from a larger number Duke[1] in 1924 and 1925 developed the concept of physical allergy although urticaria due to cold was recognized long before Duke s work He used the term *physical allergy* to designate the type of reaction—nasal bronchial cutaneous— which simulates in general character the inherited human idiosyncracies commonly classed as pollen disease and food and drug idiosyncracies but which is caused by physical agents such as light heat cold mechanical irritation freezing burns and mental or physical effort The manifestations resulting from exposure to such agents have become well recognized but the nature of their cause continues to be questioned[3, 7] In order to prove an immunologic mechanism in their causation there has been repeated search for specific skin transferable antibodies in the serum of affected patients[8, 14] or the production of anaphylaxis in experimental animals[5] Positive passive transfer has been demonstrated in a significant number but not all cases of cold and light urticaria[1, 16] *Passive transfer never has been demonstrated* in patients with generalized heat sensitivity[4] The demonstration of specific reagins transferable from the serum of the patient to the skin of a normal individual gives substantial but not absolute and final support to the belief that in these instances an allergic mechanism is involved in the production of the symptoms Sherman and Seebohm[9] in a case of marked cold sensitivity showed that more than one protein component of the patient s serum was necessary to effect a transfer of local sensitivity

Notwithstanding these positive findings other evidence has been presented to show that the symptoms of physical allergy may be mediated through a nonallergic mechanism involving excitation of peripheral nerves with the release of acetylcholine involving the direct release of histamine or possibly involving the generation of toxic substances in the tissue as a direct effect of the physical agents involved[4-6, 17-19] Horton and his coworkers[18, 1] demonstrated a typical rise in the secretion of gastric hydrochloric acid associated with a rise in the blood histamine content during and after an attack of cold urticaria They felt that the whealing in cold urticaria was similar to that produced by histamine and that the effect of the cold stimulus was mediated by histamine Others[6] have offered clinical evidence suggesting that urticaria provoked by emotion or exercise or warming the body is due to the release of acetylcholine In the case of light sensitivity the possible presence of photodynamic substances in the blood and in the skin may explain the reaction[2] In some instances antihistamines have been helpful in controlling the symptoms of cold heat and light urticaria[8, 3, 9]

The following hypotheses commonly are offered to explain the mechansim of physical allergy

1 Under the influence of the physical agent some substance is formed or liberated in the tissues and serves as a true allergen

2 The physical agent stimulates the combination of antigen and antibody already present in the tissues

3 The action of the physical agent through the medium of the central and peripheral nervous systems leads to the release of acetyl choline or histamine is released directly under the stimulus of the physical agent or some other chemical substance is released This hypothesis of course implies a nonimmunologic basis

No theory yet presented is fully adequate in explaining all the observed phenomena clinical and experimental It would be wise to exercise some reservation about the allergic nature of some cases of physical allergy

SYMPTOMS

The symptoms produced by physical agents fall into two cate gories In one the manifestations are confined to the area of contact with the agent in the other they are systemic or widespread Duke originally called the first category contact reactions and the second reflex like reactions which he theorized might be due to a dis turbance in the heat regulating mechanism He believed that the nose and bronchial mucosa are more commonly involved than the

skin Among the symptoms that have been ascribed to the effects of physical agents are urticaria[8, 9, 14, 15, 30] angioedema[29] asthma rhinitis migraine[3] cardiac arrhythmia[3] syncope[19, 20] purpura[13, 31] hemoglobinuria[16] abdominal pain[2] and paroxysmal diarrhea[3] Eosinophilia occurs if there is no other accompanying allergy only when the reaction is widespread Many patients reacting to physical agents give a positive family history for allergy The presence of cold hemolysins cold agglutinins or cryoglobulinemia (cold precipitable serum globulin which dissolves on warming) is not essential Urticaria is the most common symptom Cold is the most common physical agent causing symptoms

COLD SENSITIVITY

Some cases of cold allergy are actually due not to cold but to the *reaction of heat following exposure to cold* The common causes of cold reaction are exposure in cold weather swimming holding iced drinks taking cold showers and drinking cold fluids The urticaria resulting from cold may be local or generalized Many patients exhibit local symptoms followed by systemic manifestations The wheals of cold urticaria have few pseudopods and the whealing is more extensive than in the diffuse reaction to heat Difficulty in swallowing abdominal cramps swelling of the oral mucosa and edema of the glottis may follow the drinking of cold fluids The occasionally reported drowning of a good swimmer may be the result of syncope due to contact with cold water

Immersion of the hand of a cold sensitive individual in water at 45 F for six minutes may be followed by redness and swelling of the hand with systemic symptoms such as flushing of the face fall in blood pressure and acceleration of the pulse occurring after a latent period of three to six minutes[9] Recovery from such reaction takes ten to fifteen minutes The temperature levels at which symptoms appear vary considerably At times the reaction is extremely rapid A cold site that has reacted once will be less reactive to an application of cold on the following day The diagnosis of cold sensitivity depends on the history confirmed by testing with cold water by any one of several methods such as applying test tubes containing water at approximately 45 F for six to ten minutes and waiting for wheals to appear at the site after a latent period of several minutes or less This is illustrated in Fig 44 1

The treatment of cold sensitivity consists primarily of avoiding exposure The use of antihistamines may be helpful at times but is often valueless Epinephrine injected into a wheal controls the

reaction but given at a distance is ineffective Hyposensitization by exposing the hand or hands in water at progressively lower temperatures may be helpful [21] The hand is immersed in water at about 63 F for two to five minutes several times a day and the temperature of the water is gradually reduced on successive days to about 45 F if the patient tolerates the lowered temperatures Horton has suggested nonspecific hyposensitization with histamine beginning with 0 1 mg or less twice daily and continuing for two to three weeks

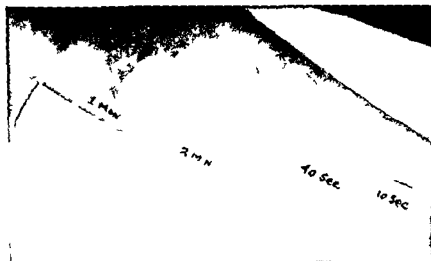


Fig 44 1 Cold urticaria after application of ice cube to forearm (Courtesy of W B Sherman N Y C)

HEAT SENSITIVITY

The incidence of urticaria caused by heat is less common Among 983 cases of skin allergy Sigel [31] found only 22 instances caused by heat exertion or emotion making an incidence of 2 2 per cent among dermatologic patients The symptoms accompanying *exertion* or emotional tension are the result of the heat generated under these circumstances The usual causes of heat reaction are hot baths exposure to the sun eating hot foods sitting in a warm room strenuous exercise and excitement The generalized urticarial reactions to heat exertion and mental stress [41] more recently have been referred to as cholinergic urticaria [6] since they are believed to be due to the liberation of acetylcholine Patients with generalized heat urticaria remain resistant to further stimulation by heat for as long as twenty four hours The characteristic wheals are seldom

larger than 5 mm in diameter and occur in the center of bright flares 4 to 8 cm in diameter Attacks of generalized urticaria can be induced in heat sensitive patients by placing them in a cabinet or by having the patient put one leg in hot water In the latter case hives appear over the entire body except the immersed leg which merely becomes flushed Among the general manifestations observed in heat sensitivity are urticaria papules flushing prickling and burning sensations salivation faintness abdominal pain loose stools migraine asthma tachycardia and collapse

Heat sensitivity reactions are more common during the winter months Erythema is not an invariable accompaniment of the wheal ing The distribution of the skin lesions is often widespread includ ing the scalp palms soles shoulders and back Dermographism is present but not marked Eosinophilia is uncommon but may occur in severe reactions The diagnosis is made on the basis of history and confirmed by test

In general treatment is not satisfactory In treating an acute episode any cooling agent applied to the skin will give some relief —ether alcohol exposure to cool air removing clothing Epinephrine is not dramatically helpful Prophylactically in addition to avoiding precipitating causes an attempt may be made to increase tolerance by exposing the subject to gradually higher temperatures beginning by placing the hand in water at about 99 F and increasing the temperature to 110 F followed by a hot bath at 100 F[31]

LIGHT SENSITIVITY

Patients sensitive to light exhibit urticaria acute or subacute inflammatory reactions of the skin and at times lesions suggestive of neurodermatitis The lesions are usually confined to the exposed areas especially the face Widespread reactions of a reflex like type with sneezing and rhinorrhea have been described by Duke Those exhibiting urticarial lesions react to wave lengths between 3 900 and 5 200 angstrom units The time of exposure needed to evoke a re action is usually a few minutes less often several hours In some in stances reactions occur only after photosensitizing agents have been ingested (sulfonamides) or applied to the skin (tars) Sensitivity to x ray and other forms of irradiation has been reported[3, 9]

In light sensitivity too the diagnosis depends on the history and the reproduction of the lesions by exposure Treatment is generally unsatisfactory Among the procedures that have been tried are changes of *environment wearing tinted glasses staying* indoors avoiding known photosensitizing substances coating the skin with

agents capable of filtering out the injurious rays and desensitization as done by Hurst[34]

MECHANICAL IRRITATION

In some individuals slight irritation of the skin is followed by marked erythema and scratching is followed by whealing Duke regarded this type of reaction as similar to the local types of urticaria caused by light and cold Irritation over an extensive area produces generalized itching and urticaria This type of response to mechanical irritation can be prevented by epinephrine This reaction is classified under the heading of urticaria dermographia

It is most important to differentiate the specific types of reaction to physical agents discussed above from the various manifestations evoked secondarily in allergic individuals by the endless number of nonspecific excitants such as walking against a wind other forms of exertion or the inhalation of irritating fumes

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James H Barnard

45

ALLERGY TO INSECT STINGS AND BITES

The severe[1-6] and sometimes fatal[7-13] reactions* to a single insect sting occurring within a matter of minutes are of interest and importance not only to physicians but also to hospital industrial and first aid personnel Present evidence indicates that such a reaction is primarily allergic in nature[14-17] hence prophylactic immunization of persons known to be sensitive to insect stings should be of value Numerous articles in the literature provide bountiful evidence that such is the case[18-26] It is the purpose of this chapter (1) to review briefly the problem and literature (2) to outline a plan for immunization of sensitive persons including some clinical data and (3) to offer a plan for emergency treatment in cases of anaphylactic response to insect stings

Before dealing with the above matters specifically it is worth while to point out that the allergic reactions may consist of urticaria angioneurotic edema rhinitis asthma or vascular collapse singly or in combinations While a fatal outcome of such reactions is unusual it does occur and postmortem data recently provided by a state Department of Health[27] confirm an allergic type of reaction in three such cases The fact that one sting is capable of producing an anaphylactic response shows the allergic character of the reaction When such a reaction is the result of many stings the ques

King Menes of Egypt met his death through the sting of a wasp or hornet circa 2641 B.C. This is the first recorded allergic disease (Waddell L A Egyptian Civilization London Luzac and Company 1930)

tion arises whether it is primarily allergic or a different toxic type of response

The following data from these fatal cases show the violence of the response in very sensitive individuals One death was from a wasp another from a yellow jacket and the third from a bee sting The ages of the victims were forty six thirty seven and twenty eight years respectively All were males Death occurred in two cases within thirty minutes The duration of illness in the third was not given

The cause of death in the first case was recorded as congestive heart failure and anaphylactic shock due to wasp sting Postmortem findings in the second case included general visceral congestion with petechial hemorrhages due to toxemia from yellow jacket stings Other significant conditions found were acute gastroenteritis and myocarditis Their possible relation to the stings was not indicated The cause of death in the third case was reported as suffocation due to edema of the larynx from bee sting Similar findings have been reported by other observers [7, 13]

Fortunately such extreme sensitivity is rare However the degree of reaction to a sting may increase from one exposure to another and since there are a fairly sizable number of persons mildly sensitive to stings prophylactic education of these individuals is also worth while An editorial in the *Journal of the American Medical Association* in 1954 made suggestions along this line -

The following report illustrates the problems under discussion

Mr R J P aged fifty three was subject to urticaria from shellfish to periodic migraine to poison ivy sensitivity and to chronic rhinitis His father had migraine The history revealed that three yellow jacket stings on his right hand had been followed by immediate swelling of the entire right arm which gradually subsided Two years later he was stung on the left hand by a wasp the entire arm became swollen and the patient felt dizzy the reaction again slowly disappearing The following year the patient was stung on the left wrist by a wasp The arm immediately became swollen He had a strong urge to defecate and as he reached the toilet he lapsed into coma and had an involuntary bowel movement and emptying of the bladder He gradually regained consciousness and recovered

The reactions to intradermal skin tests with approximately 0 015 ml of extracts of powdered whole bee wasp and yellow jacket standardized on a protein nitrogen basis are listed in Table 31

The patient was immunized with a schedule of doses comparable to those used in a group A pollen case that is one which showed a marked skin test with an extract containing 10 protein nitrogen units per milliliter The tests suggested that this man should have been able to tolerate a group B schedule but because of a tendency to urticaria headache

TABLE 31 REACTIONS TO INTRADERMAL SKIN TESTS WITH INSECT EXTRACTS

Insect	Reaction to protein nitrogen units per [illegible]		
	1	10	1[illegible]0
Wasp	Negative	Slight	Marked
Honeybee	Negative	Slight	M[illegible]
Yellow jacket	Slight	Moderate	Marked

and large local reactions from the injections a group A [illegible] was settled on The dosage schedule for a group A [illegible] Table 32

TABLE 32 DOSAGE SCHEDULE FOR GROUP A POLLEN [illegible]

Dose number	Number of protein nitrogen units
1	5
2	10
3	15
4	25
5	3
6	50
7	75
8	125
9	175
10	200
11	300
12	500
13	600
14	800
15	1000
16	1,200

The immunization has been maintained with a [illegible] approximately 1 200 protein nitrogen units of [illegible] protein nitrogen units each of wasp and bee extra[illegible] excessive local reactions It is planned to contin[illegible] round top dosage schedule as long as the patient [illegible] tive tests by yearly retesting

A year after treatment began the patient was [illegible] wasp and immediately took 8 ml of elixir of [illegible]

jection of 0 5 ml of epinephrine 1 1 000 Nothing happened except ex treme tremor and a headache for several hours thought to be from the epinephrine There was only a slight area of redness and itch at the site of the sting and practically no swelling He is now willing to give his immunity a real clinical trial without other therapy if possible should he be stung again

Numerous other cases are under similar perennial therapy One young man of sixteen had been stung several times without apparent effect In 1953 he was stung by a yellow jacket with no reaction but about three weeks later after several yellow jacket stings he devel oped an immediate generalized angioneurotic edema requiring drastic measures for symptomatic control including epinephrine a tourniquet and antihistamines In 1955 during his second year of perennial immunization therapy against wasp yellow jacket and honeybee this patient was stung by a wasp without reaction except for a slight wheal at the sting site

Loveless at the New York-Cornell Medical Center has been doing research on this problem In work she reported at the annual meeting of the American Academy of Allergy in February 1954 and later published [5] along with material being developed she was able to demonstrate protection in sensitive patients from a series of injec tions with suspensions containing increasing numbers of the insects sting sacs The protection has been confirmed by a direct challenge when the patients were willing to submit to an actual sting from a live insect Further evidence of protection was shown by Loveless in the demonstration of a specific blocking antibody after treatment with the sacs [8]

Of biologic interest [9] in this problem are the following facts

1 Entomologically hornets and wasps are identical

2 Yellow jackets are thought to have the more powerful venom

3 The venom consists of an alkali and an acid which merge at the base of the stinger Sometimes only one factor is injected in the sting and the resultant reaction is less severe also the proportions vary

4 While wasps food is largely protein and bees food is nectar and honey there is thought to be very little difference between their venoms

5 When the bee stings its sac is pulled from the abdomen and the insect dies whereas wasps and yellow jackets may sting again and again

6 Yellow jackets make their nests in the ground or adjacent thereto as in rock piles [10] Wasps make their nests in higher places such as ceilings Their nests are conical or ball shaped

Previous immunologic and allergic studies on extracts of insects

and their stings[19, 1] seem to indicate that there is little if any demonstrable difference in reactivity between extracts made from the abdomen containing the sting sac (in the bee) and those from the anterior part of the body Likewise in mosquitoes extracts made from the head and thorax containing the salivary glands differ little if at all in reactivity from those of the rest of the body In view of the above and since separating sting sacs from the other body structures is difficult and the sac wall remains anyway extracts from the entire insects seem more practical particularly when satisfactory protection is obtained by that method On the basis of such findings insect extracts are standardized for clinical use according to their protein content The difficulty of obtaining sufficient pure venom for use alone in extracts is easily appreciated

Since a single bee or wasp sting in a very sensitive individual may be sufficient to cause death in a matter of minutes it is most important that the patient and his physician have a plan of procedure ready should the emergency arise Patients known to be extremely sensitive to stings should be thoroughly instructed and provided with remedial drugs and measures for immediate use even before summoning the physician

As an adequate emergency program for such a patient a small kit should be prepared containing an ampul of epinephrine 1 1 000 a vial of injectable antihistamine a tourniquet large enough to go around the thigh and a sterile 1 ml hypodermic syringe and needle Instruction and demonstration should be given by the doctor to the patient in the use of the tourniquet (or a piece of cloth in an emergency) and epinephrine injection of 0 5 ml proximal to the tourniquet or beneath and around the sting If the sting is on the trunk or head where no tourniquet can be applied the injections should be carried out immediately Next instructions call for the injection of a full dose of an antihistamine in another area Since the peak of a reaction will be reached within a half hour and one of the serious effects of anaphylactic shock is circulatory collapse the patient should be cautioned against a long run or other excessive physical strain Maintenance of warmth is helpful If the condition is not improved after about fifteen minutes the remaining 0 5 ml of epinephrine should be given Finally a careful explanation of the expected effects from the epinephrine will be helpful An antihistamine may be given orally instead of by injection if the patient is known not to be very sensitive and is not in danger clinically (see Chap 58)

Two reports of acute anaphylactic reactions from ant bites should also be mentioned[31, 32]

Besides the severe immediate type of allergic reaction to stings

there may occur a mild immediate type of allergic wheal to bites from mosquitoes[0 34 35] ants[36] fleas of different types[3 38] chiggers[39] lice[40] and bedbugs[41] Accompanying these reactions or replacing them there may be a delayed type of local reaction at the site of the bites[33] The latter is most frequently found with mosquito bites and may progress to vesiculation of the lesion In these cases there is no systemic effect of any severity The treatment consists of anti histamines taken internally for the itching plus creams and lotions with the same drug or with hydrocortisone or fluorocortisone for local application and these usually control the condition satisfac torily Extracts of these insects are available if immunization appears necessary

One other type of allergy to insects while not strictly within the scope of this chapter deserves to be mentioned at this point A form of allergic response caused by sensitization to emanations from insect bodies and their excreta results in allergic reactions in the respiratory tract and the skin This reaction is more fully described in an article by Feinberg Feinberg and Benaim Pinto[4] In addi tion the reader is referred to an excellent bibliography consisting of 68 articles covering the literature on insect allergy up to 1944 by E A Brown[43] which covers both phases of the problem Gail lard[44] has reported allergic reactions to aphids and Shields[45] has described sensitization to *Triatoma sanguisuga* (kissing bugs) from its bites It is likely that many cases of sensitization caused by in sects (emanations secretions bites and stings) go unrecognized The allergist needs to become more vigilant in this direction

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ALLERGY TO DRUGS IN GENERAL

In general the causative agents of allergic disease are substances with which the patient comes in contact naturally such as foods and environmental dusts and which are not harmful to the nonallergic person In the case of allergy to drugs one must consider a group of chemically and biologically active substances with which there is normally no contact and which have definite pharmacologic effects on the normal person

When an untoward effect follows the therapeutic use of a drug the distinction between its toxic action and an allergic reaction resulting from acquired hypersensitivity is not always easy Allergic phenomena in general result from reaction of antigen and antibody and the existence of antibodies of various types can be established in many allergic diseases In the cases of allergy to drugs however this evidence of an allergic mechanism is only rarely demonstrable presumably because the drugs act as haptens rather than complete antigens Likewise the types of skin tests applicable in the diagnosis of inhalant and food allergies only occasionally show positive reactions in drug allergy For these reasons the diagnosis of reactions to drugs as manifestations of allergy is usually based on the clinical observation of acquired sensitivity

This is apparent when a patient at first shows no adverse reaction to a drug but after taking the same medication for a period of days or weeks develops a reaction differing from the usual toxic

effects and then subsequently shows the same reaction to smaller doses

Most of the common manifestations of allergy such as asthma rhinitis contact dermatitis and urticaria may be caused by drugs In addition a considerable variety of reactions which rarely if ever result from allergy to naturally encountered allergens may be caused by hypersensitivity to drugs Such reactions include fever a wide variety of skin rashes hepatitis leukopenia and thrombocytopenic purpura

Of the drugs causing asthma and rhinitis aspirin is by far the most important offender although many others both synthetic compounds such as sulfonamides and arsphenamine and proteins such as papain are occasional causes It is important to remember that in susceptible persons extremely severe asthma may result from ordinary doses of aspirin Except in the case of the protein drugs skin tests rarely yield positive reactions Attempts to perform scratch or intracutaneous tests with aspirin on such individuals are both futile and dangerous since they may produce violent asthma without eliciting any local reaction The diagnosis must be based largely on the history If there is a clear story of asthma occurring regularly after the ingestion of aspirin the patient should be considered allergic without attempting any confirmatory test Patients known to be allergic to aspirin should be warned of its presence in most proprietary remedies for headaches and colds

The list of drugs which may cause urticaria is a long one including penicillin streptomycin aspirin sulfonamides barbiturates insulin liver extract and others The most common cause penicillin is discussed in the succeeding chapter Skin tests are of little value in the diagnosis of drug urticaria When a patient taking various drugs develops urticaria the best procedure is to stop or change all of the medications until the effects are observed

Drug fever is a common complication of treatment with sulfonamides thiouracil para aminosalicylic acid arsenicals mercurial diuretics and anticonvulsant drugs Many other drugs are less frequent causes The onset typically occurs a week or more after the first use of the drug that is after sensitization has developed The fever may reach 102 to 105 F and may be continuous or intermittent depending on the frequency of dosage When the offending drug is discontinued the fever subsides as soon as it has been eliminated from the body usually in a few days After sensitization has occurred subsequent use of the same drug may produce fever in a few hours (Fig 46 1) Drug fever may or may not be accompanied by a skin rash which most often is maculopapular or erythematous The

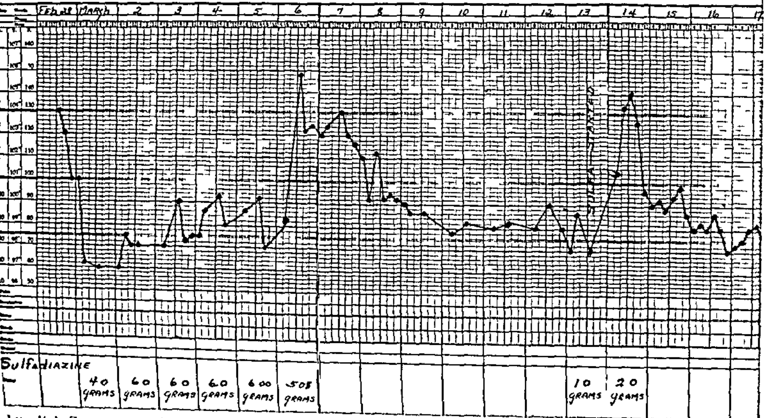


Fig. 16-1 Temperature chart in a case of drug fever due to sulfadiazine. Note sharp rise in fever on sixth day of treatment falling in three days after drug was stopped. There was subsequent recurrence within 24 hours after trial dose.

leukocyte count may be normal or increased with a predominance of polymorphonuclear neutrophils Eosinophils are rarely increased The diagnosis may be suspected if unexplained fever develops during the administration of any of the commonly causative drugs and subsides when they are discontinued

If the drug which causes fever is promptly eliminated the whole episode is usually mild and the patient suffers little discomfort However histologic studies of patients dying during the course of the fever show that it is accompanied by widespread lesions involving many of the vital organs One of the commonest lesions is arteritis which involves the smaller arteries and arterioles with fibrinoid



Fig 46 2 Dermatitis medicamentosa due to sulfadiazine

degeneraton of the media and perivascular infiltration similar in microscopic appearance to periarteritis nodosa as pointed out by Rich [1] The myocardium is often involved with edema between the muscle fibers and infiltration about the small vessels Foci of necrosis infiltrated with wandering cells may be seen in the liver spleen kidneys and lymph nodes and less often in other organs Apparently these lesions heal quickly if the drug is discontinued but they indicate the potential danger of further use Continuing the administration of sulfonamides and other drugs in the presence of drug fever has led to fatal results in some cases

While many types of skin rashes may be due to drug allergy the

two commonest forms are dermatitis medicamentosa due to systemic medications and contact dermatitis due to topical applications Both are evidence of acquired sensitization and characteristically occur a week or more after the first contact with the drug Dermatitis medicamentosa may be due to any of the drugs mentioned as causes of drug fever and also to barbiturates gold salts and many others It usually begins as a maculopapular rash which particularly affects the trunk (Fig 46 2) It is sometimes but not always accompanied by drug fever If the drug is stopped in the early stages the rash fades promptly except when due to slowly excreted drugs such as gold



Fig 46 3 Positive patch test with sodium sulfadiazine (same patient as in Fig 46 2)

salts and arsenicals If the causative drug is continued the rash tends to become confluent and may progress to exfoliative dermatitis Skin tests are of limited value in proving the etiology of dermatitis medicamentosa but if the drug is one that is readily absorbed through the intact skin the patch test may be positive Fig 46 2 illustrates dermatitis medicamentosa due to sulfadiazine A positive patch test with the drug was obtained as seen in Fig 46 3

Contact dermatitis may be produced by sulfonamides antibiotics local anesthetics antihistaminic drugs mercurial ointments and many other topically applied drugs It is characteristically vesicular and does not differ materially from contact dermatitis due to poison

ivy or industrial contactants As a rule the patch test with the offending drug is diagnostic

Less common forms of dermatitis due to drugs include erythema nodosum most often caused by the sulfonamides and antithyroid drugs fixed drug eruptions resulting from sensitization to phenolphthalein aminopyrine barbiturates and arsenicals and acneiform eruptions produced by iodides and bromides

Hepatitis produced by arsenicals sulfonamides cinchophen gold salts and Atabrine shows the features of an acquired sensitization and is often accompanied by other manifestations of drug allergy such as fever and dermatitis On the other hand carbon tetrachloride and other chlorinated hydrocarbons cause hepatitis by direct toxic action A distinction between these two types of drug hepatitis and infectious hepatitis is not always easy but the occurrence of jaundice during the administration of any of the above drugs is reason enough to discontinue them The physician should also bear in mind that jaundice due to drugs (particularly arsenicals and chlorpromazine) may have the chemical features of obstructive jaundice.

Leukopenia and agranulocytosis may result from the use of aminopyrine arsenicals thiouracil sulfonamides gold and anticonvulsive drugs Except for gold and arsenic these drugs are rather quickly eliminated from the body and the tendency is to recover within a week after the drug is discontinued During the stage of marked leukopenia antibiotics are essential for the control of infection Thrombocytopenic purpura is most often caused by Sedormid arsenicals gold and sulfonamides Recovery generally follows excretion of the drug

Since skin tests are rarely reliable and antibodies can only occasionally be demonstrated the diagnosis of drug allergy depends chiefly on knowledge of the types of allergic reactions apt to be produced by various drugs and alertness in recognizing the causative relationship While the most frequent causes of various manifestations have been mentioned these lists are not complete For a list of other drugs reported to cause these conditions the reader is referred to Alexander s *Reactions with Drug Therapy*

Since most of the manifestations of drug allergy tend to subside as the causative agent is excreted the most important point in treatment is prompt discontinuation of the medication In the case of arsenic and gold the elimination is slow and the occurrence of serious allergic reactions to these drugs calls for the use of BAL to aid detoxification and excretion For symptomatic treatment of drug allergies cortisone and corticotropin are the most effective measures They are of little value however in hepatitis and agranulocytosis

Desensitization with drugs involves some risk of reactions and is only occasionally effective Some favorable results have been reported however especially with para aminosalicylic acid

Drug allergy tends to persist over long periods of time and further use of the drug which has once produced a reaction should be avoided if at all possible In cases of dire need where there is no possible substitute medication the relative risks of using or withholding the drug must be carefully weighted

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ALLERGY TO PENICILLIN

Problems of drug intolerance demand increasing attention most unpredictable is that form of intolerance caused by allergy Of all remedies apparently the most innocuous as well as the most magically potent penicillin has nonetheless proved to be an unexpectedly frequent sensitizer in man The range of sensitivity phenomena attributable to penicillin has extended to include progressive vascular reactions[1] and the more urgent danger of fatal and near fatal anaphylaxis[4,7] Whereas the other antibiotics commonly in use in everyday practice induce only infrequent and relatively minor allergic reactions to the physician and to the surgeon penicillin has become the problem antibiotic because of its sensitizing capacity[8]

CLASSIFICATION OF PENICILLIN ALLERGY

Type I Delayed The delayed reaction is the most common and it is thus called because of an incubation period usually of from 7 to 14 days The minimum interval may be five days the maximum perhaps about eight weeks This is the response of initial sensitization and no previous exposure to penicillin need have taken place It may simulate serum sickness with the typical triad of eruption fever and joint pains While any of these manifestations may dominate the clinical picture urticaria is by far the most common (Table 33)

Type II Accelerated and Immediate Accelerated and immediate reactions are much less frequent and occur only in patients who

TABLE 33 TYPES OF ALLERGIC REACTION TO PENICILLIN

Type	Incident	Incubation period	Major manifestations	Skin tests	Course and treatment
I Delayed	Common	5 to 21 days	Urticaria fever arthralgias serum sickness like syndrome	Usually negative delayed test may be positive following this reation	Usually 3 days to 3 weeks occasionally prolonged to 1 year antihistamines ephedrine ACTH and steroids
IIA Accelerated	Infrequent	2 to 48 hours	More intense reactions as in Type I angioedema	Delayed test may be positive (tuberculin like type)	Usually several days epinephrine aqueous and in oil and as in Type I
IIB Immediate	Rare	30 seconds to 2 hours	Pruritus urticaria angioedema asthma pulmonary edema anaphylactic shock	Immediate test often 4 plus positive (scratch test safest)	Minutes or hours epinephrine repeatedly antishock measures dangerous may be fatal
III Hyperergic	Uncommon	As in Type I or IIA	Purpura bullae exfoliative dermatitis ECG and renal changes Loeffler s syndrome progressive angiitis locally Arthus phenomenon	Usually negative	Usually self limited rarely fatal progressive may follow I or IIA prolonged ACTH or steroids for complete suppression
IV Erythematovesicular or id like	Frequent	1 to 3 days occasionally 6 days	Hands feet groins erythema papulovesiculation marked pruritus silent sensitivity in 5% of adults	Delayed test often positive (eczematous type)	1 to 3 weeks steroids and medications topically
V Contact dermatitis	Frequent	5 to 21 days	Erythema and papulovesiculation dermatitis venenata	Patch tests often posit e	Several days or weeks sterods and topcal applicat ons

Th conj n t al test n y be an a l l t o v l u ful p t on ry p oc lu

have been sensitized by previous exposure to penicillin They represent the reaction of reexposure to antigen and hence as a recall phenomenon are characterized by the shorter incubation period from which they derive their name This may vary from several hours to two or three days in the accelerated type and from seconds or minutes to two hours in the immediate type Clinically these may be mild or severe more often the latter Hyperacute serum sickness *angioedema asthma and anaphylaxis may occur* Immediate reactions may range from simple pruritus or apparently trivial urticaria to the full blown picture of intractable and fatal shock



Fig 47 1 Erythematovascular or id like (Type IV) penicillin eruption affecting the hands

Type III Hyperergic Hyperergic reactions are rare and include more intense vascular cutaneous and visceral phenomena which may follow Types I or II accelerated reactions Bullous exfoliative and purpuric eruptions may be seen [9] Loeffler s syndrome and reversible renal and myocardial involvement occur [10, 11] Progressive diffuse angiitis with fatal termination has been reported [13] Instances of systemic lupus erythematosus have been ascribed to penicillin allergy [1] and a positive LE test has been reported in patients with

allergic reactions to penicillin[13, 14] Rare local reactions resembling the Arthus phenomenon may belong to this category

Type IV Erythematovesicular The erythematovesicular or id like reactions are second to Type I in incidence They are likely to appear after a somewhat short incubation period several hours or days after penicillin administration Bright pink very pruritic ery



Fig 47 2 Erythematovesicular or id like (Type IV) penicillin eruption of the feet (same case as Fig 47 1)

thema at times with papulation or even vesiculation affects particularly the groins hands and feet (Figs 47 1 and 47 2) It may become generalized subsiding with a fine branny desquamation It probably represents activation of a previously silent sensitivity induced by fungous disease of the skin[1, 16] In favor of this concept is the id like appearance of the eruption its characteristic distribu

tion on sites of predilection for dermatomycosis and finally the demonstration that five per cent of adults never before exposed to penicillin show a positive 24 to 48 hour delayed skin test to the antibiotic[16, 17]

The first three types of penicillin allergy are independent of presensitization by dermatophytes and are not related to previous dermatophytosis The separation between these two forms of penicillin sensitization is indicated by the consecutive occurrence in the same patient of two clinical reactions the erythematovesicular preceding the urticarial This has been observed by the author and documented by others[18]

Type V Contact Dermatitis This is not a rarity and follows the topical application of penicillin now largely abandoned or on occupational exposure among those who handle penicillin This includes not only doctors and nurses but also the personnel of penicillin manufacturing plants[19] Penicillin ointments are now scarcely ever used for surface skin infections Ophthalmologists have particularly discarded penicillin ophthalmic ointment The eruption may be acute like a typical dermatitis venenata or may simulate a more chronic eczema The stomatitis which follows the use of penicillin troches is likewise a manifestation of a contact allergy

This rather benign contact allergy of the epidermal type must not be confused with a violent systemic sensitization which may likewise affect doctors nurses and handlers of penicillin probably acquired through inhalation of the antibiotic Such persons react with immediate erythema and pruritus after even trivial contact with penicillin and belong in the anaphylactic Type II category

SPECIAL CHARACTERISTICS OF PENICILLIN ALLERGY

1 Allergic reactions to penicillin appear to be both less frequent and less severe in children than in adults[0] although shock reactions in children have been reported[1] Erythematovesicular reactions are more common in men than in women and scarcely ever affect children

2 Penicillin treatment may be continued in some instances despite the occurrence of a mild urticarial Type I or erythematovesicular reaction Such persistence in treatment is justified only when the reaction is readily controlled by antiallergic therapy and when there is an urgent indication for penicillin[20, 3] Thus cases of subacute bacterial endocarditis have been carried to complete cure despite moderate allergic reactions In exceptional instances even

more intense reactions may be controlled by steroid therapy to permit curative therapy with penicillin as for example in the treatment of syphilis [3]

3 A single episode of a Type I urticarial or serum sickness-like reaction does not constitute an absolute and permanent contraindication to all subsequent penicillin treatment While it is safer to treat such patients with nonpenicillin substitutes whenever possible it should be realized that most of them do not develop persistent penicillin allergy and many accept penicillin without difficulty at a later date [4] [9] Such a resumption of tolerance for the antibiotic may at times be of crucial clinical value e g in the management of subacute bacterial endocarditis This important clinical point should be known to the physician who must understand however that reinstitution of therapy with penicillin can only be carried out after suitable *precautions involving preliminary skin* tests and multiple small graded trial doses

In contrast with Type I reactions those of the Type II III and IV categories should be considered almost absolute contraindications to further penicillin treatment Any history even suggestive of an immediate or shock reaction rules out the use of penicillin completely

4 Penicillin urticaria may be unexpectedly protracted in course lasting up to a year or more Occasionally rather acute episodes of a serum sickness-like reaction may recur for months It has been suggested that the small quantities of penicillin occasionally present in milk *contribute to this chronicity*

PENICILLIN SKIN TESTS IMMUNOLOGIC OBSERVATIONS

Skin tests with penicillin have been in much dispute In most forms of drug allergy tests with the drug are uniformly unsuccessful It is not surprising therefore that in penicillin allergy the skin test most often gives negative reactions [6] Nonetheless there is now well-documented evidence that the positive *immediate* skin test read at 15 minutes and most safely elicited by the scratch method or by passive transfer is a definite warning signal of potential anaphylaxis [5-7] [7] Crystalline penicillin G solution is preferable for these tests although procaine penicillin suspension may also elicit positive reactions When the history suggests the possibility of anaphylaxis the test is most safely carried out with graded dilutions beginning with 100 units per ml increasing to 50 000 units per ml

If the scratch test is negative then intracutaneous tests may be carried out with dilutions of penicillin varying from 1 000 to 50 000

units per ml employing 0 02 ml as in standard allergy testing to produce a just visible test wheal The reaction of increased wheal and flare is at its height in 15 to 20 minutes The use of a conjunctival test to supplement the scratch test is discussed in the section on prevention of anaphylaxis

The positive *delayed* skin test reaction read like a tuberculin test at from 24 to 48 hours for erythema and edema was first described by Welch and Rostenberg[17] The incidence of this type of reaction rises sharply among those who have had a previous reaction to peni-



Fig 47 3 Strongly positive delayed (24 to 48 hours) eczematous reaction to penicillin skin test

cillin[5] This observation however is still a matter of dispute[6] The author has observed the delayed skin reaction to be associated at times with persistent penicillin allergy of the urticarial type[2] although it is more common in Type IV erythematovesicular reactions This test is elicited by the intracutaneous injection of 0 1 ml of crystalline penicillin G solution or aqueous procaine penicillin in a concentration of 10 to 50 000 units per ml (Fig 47 3) It is preferable as a safety measure to do the delayed test after the immediate skin tests have been carried out In contact dermatitis similar solutions or suspensions in a concentration of 100 000 unit

per ml may be used for patch testing Negative skin tests with penicillin do not exclude allergy or even the threat of anaphylaxis When indicated and with suitable precautions the presence or absence of penicillin sensitivity can then only be explored by means of carefully graded trial doses of the antibiotic

As in general drug allergy antibodies to penicillin have not been demonstrated except in the immediate and anaphylactic reactions in which passive transfer tests may be positive indicating the presence of reagins or skin sensitizing antibodies[30] Technics for the demonstration of penicillin antibodies in vitro were futile until the recent report of the agglutination of erythrocytes by certain sera in the presence of penicillin[31] This interesting phenomenon requires further investigation and thus far has not been correlated with penicillin allergy

Penicillin is considered to function as a hapten becoming antigenic after it reacts with body protein In contact dermatitis and in Type IV erythematovesicular reactions penicillin is assumed to interact with an epidermal protein such as keratin In the Type I II and III reactions a serum protein is probably involved Recent observations suggest that perhaps penicillin combined with gamma globulin may provide a more suitable diagnostic test antigen for skin testing in penicillin allergy[3] This work awaits confirmation

PENICILLIN DESENSITIZATION

Desensitization with penicillin is occasionally useful[33] Thus it may be employed when there is definite evidence of persistent penicillin allergy in patients for whom penicillin treatment is imperative for example in syphilis or for subacute bacterial endocorditis and those who must handle it It has no place as a routine measure for the patient who has had a single Type I reaction for as already noted such patients often desensitize themselves spontaneously Desensitization may be too hazardous in patients with a history of an *immediate or anaphylactic reaction* Roberts[10] however described successful desensitization in instances of occupational penicillin asthma Such cases fall within the Type II immediate category Penicillin allergy in nurses may require desensitization[34]

In the course of desensitization of patients with erythematovesicular reactions[35] or prolonged urticarial responses[3] the positive delayed skin test was observed to convert to negativity A recent application of this method with which the author has had some success has been in refractory cases of prolonged penicillin urticaria in which all other therapy including repeated steroid and ACTH

therapy has failed to halt the reaction Desensitization is tedious and prolonged a typical schedule is shown in Table 34

TABLE 34 PENICILLIN DESENSITIZATION SCHEDULE *

Injection	Dose (units)
1	10
2	20
3	50
4	100
5	[illegible]00
6	500
7	1 000
8	1 [illegible]00
9	[illegible] 000
10	3 000
11	4 000
12	5 000
13	7 000
14	10 000
15	15 000
16	20 000
17	30 000
18	50 000
19	100 000
20	300 000

* Injections of crystalline G or aqueous procaine penicillin subcutaneous or intramuscular two or three times a week Adjust initial doses and increments to tolerance and local or constitutional reactions Final doses act as tests of capacity for full therapeutic dosage

SUBSTITUTE PENICILLINS AND PENICILLIN ANTIHISTAMINE MIXTURES

Neither substitute penicillins such as penicillin O nor penicillin antihistamine mixtures should be regarded as the solution to the problem of penicillin allergy Penicillin O is a frequent sensitizer [36] and only infrequently can be safely substituted for penicillin G *when true persistent penicillin allergy is present* [9, 37] Antihistamines added to penicillin have been shown in a controlled study [4] not to reduce the incidence of the common Type I delayed reactions They do inhibit some of the milder immediate or accelerated reactions but cannot be depended upon to prevent or control anaphylactic responses [36] This masking of the minor immediate reaction may actually be a disadvantage in that it removes a valuable

warning signal of the anaphylactic state The more violent or acute the penicillin sensitivity the more imperative is the need for *non penicillin* substitutes

PENICILLIN ANAPHYLAXIS

Allergic shock is the most feared hazard of penicillin therapy and such reactions have been described not only after the usual intra muscular injection but also following the ingestion of oral tablets via buccal absorption from troches after instillation of penicillin into an antrum from the use of penicillin ointment from an intra dermal test and even following a conjunctival test Despite increas ing awareness of this danger reports of fatal and near fatal shock reactions continue to appear [8, 38, 39] It must be borne in mind how ever that anaphylaxis is relatively uncommon in view of the enor mous quantities of penicillin employed estimated in 1956 at close to 600 000 lb annually

The full blown picture of anaphylactic shock caused by penicillin is the same as that induced by serum or other antigens In most in stances the reaction begins only minutes or seconds after exposure to penicillin The following sequence is typical there is a peculiar taste in the mouth or sensation in the tongue sneezing or strange tingling in the extremities These premonitory symptoms are quickly followed by severe constriction or pain over the chest or abdomen often with nausea or a sudden desire to defecate A chok *ing sensation dyspnea increasing with frightening rapidity frothy* sputum and cyanosis occur simultaneously with symptoms of col lapse which may lead to unconsciousness and even death The re action is so terrifying and so unexpected that the physician may be immobilized Alertness to the possible danger and awareness of the earliest symptoms may afford psychological preparedness so that crit ically valuable moments will not be lost in instituting anti anaphy lactic measures Thus a prompt reaction of pruritus or a sensation of warmth in the extremities a choking sensation a sense of weak ness or dizziness nausea or abdominal cramp like pain should put the physician on guard An increase in asthma after penicillin whether given by inhalation or otherwise may also be significant of impending anaphylaxis

The pathology of penicillin shock [40] is that of anaphylaxis as generally observed in humans [41] While some cases may show the acute emphysema of guinea pig lungs others may show only visceral hyperemia and an otherwise negative autopsy Human ana

phylaxis may be accompanied by electrocardiographic changes of myocardial involvement perhaps induced by coronary insufficiency (Figs 47 4 and 47 5)

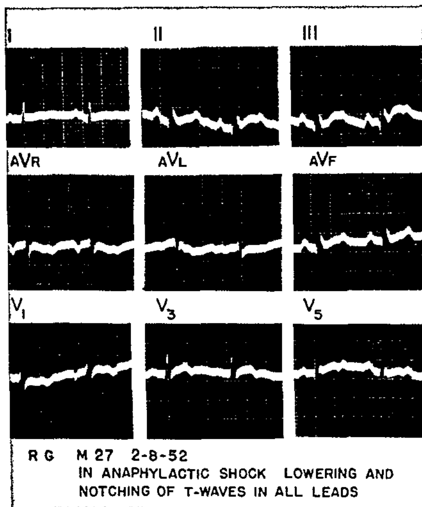


Fig 47 4 Electrocardiogram of patient in anaphylactic shock from penicillin

PREVENTION OF PENICILLIN ANAPHYLAXIS

The following precautions are suggested for reducing the incidence of allergic shock due to penicillin

1 Greater discrimination must be practiced in the use of penicillin Its futility in the treatment of the common cold and other viral infections is evident Even its supposed effectiveness in the prevention of bacterial infection is in doubt except as applied to streptococcal infection in the prevention of rheumatic fever Penicillin ought not to be used routinely pre and post operatively in non

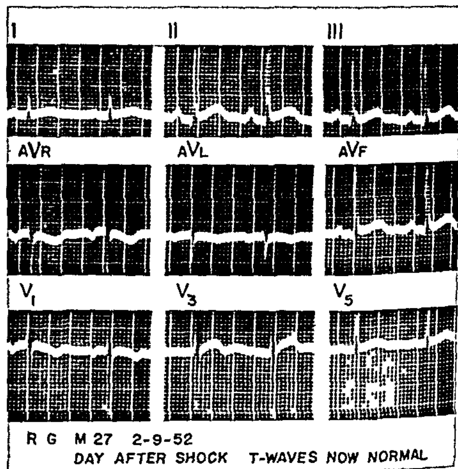


Fig 47 5 Same case as Fig 47-4 showing recovery from shock

infected surgical cases In minor bacterial infections the soluble sulfonamides and other antibiotics are preferable

The use of penicillin in the manufacture of poliomyelitis vaccine (Salk) has aroused fears of sensitization and particularly of shock reactions Early observations with the vaccine as tested against the skin and serum of penicillin sensitive persons indicated the absence

of all but minimal amounts of penicillin in the final product as available for injection[4] The vaccine thus appeared to present a negligible hazard as to penicillin allergy More recent data on the penicillin content of the vaccine indicates that it is not usually present in amounts greater than 20 units per ml However this concentration may vary from none to 200 units per ml The relative lack of penicillin sensitization from the vaccine has been borne out by an uneventful experience with millions of doses Exceptionally however reactions have occurred with urticaria erythema and serum sickness-like phenomena which are similar to those observed after penicillin administration[43, 44] Prompt response of some of these reactions to penicillinase[43] further supports the suspicion that penicillin is the most likely allergenic constituent of the vaccine responsible for these reactions Thus far there has been no report of a shock reaction induced by poliomyelitis vaccine

Accidental or inadvertent exposure to penicillin may also occur in other ways as in syringes contaminated with residues of the antibiotic[45] and also in milk which may contain variable amounts

2 Before prescribing or injecting penicillin a careful history should be taken as to (*a*) the frequency of previous penicillin treatments because it is the patient repeatedly exposed to this antibiotic who is more likely to react with shock (*b*) the uncovering of evidence of a previous allergic reaction to the antibiotic and (*c*) the detection of a personal history of allergy and especially of bronchial asthma for it is among these patients that anaphylaxis and fatalities most often occur

The character and timing of the previous reactions to penicillin are important in evaluating the probable anaphylactic hazard Accelerated and above all immediate reactions (Type II) no matter how mild must be interpreted as ominous portents of impending anaphylaxis On the other hand simple single Type I reactions are less significant as already noted and the erythematovesicular reaction is not a forerunner of anaphylaxis Repeated reactions suggest a special danger Systemic reactions on simple contact whether by absorption through skin or membranes or by inhalation as has been observed in doctors nurses and other penicillin handlers may be a form of immediate reaction indicating a highly developed anaphylactic state Paradoxically however most patients reacting with shock give no past history of previous penicillin allergy whatsoever the physician must be aware of this

3 Modifications of the usual technic of penicillin injection is suggested particularly for the first treatment dose to be administered after there has been a long interval since previous exposure to this

drug This prolonged interval measuring weeks more often months less often years since the last penicillin treatment represents the incubation period required after the sensitizing dose for establishment of the anaphylactic state just as it is observed in the experimental animal This first and most hazardous injection is best given into the outer arm rather than into the buttock or deltoid so that if need be a tourniquet can be applied proximally to delay absorption Accidental intravenous injection should be scrupulously avoided Nonetheless the author is quite convinced that such accidents rarely account for the shock reactions observed which can occur as promptly and as violently from an intradermal test dose Epinephrine solution should be at hand preferably already drawn up in a syringe

Walbott s suggestion offered years ago[46] that only the first few drops of the possibly anaphylactogenic material should be given after which there should be a 45 second pause before completing the injection has practical value A still safer precaution is the preliminary administration of 1/20th of a ml or a drop or two of the treatment strength suspension of aqueous procaine penicillin or of one quarter of an oral penicillin tablet ten minutes before proceeding with full dosage

4 A preliminary skin test may reveal the danger of impending anaphylaxis It is safest to begin with a scratch test and a clearly positive reaction is considered to contraindicate the administration of penicillin As a routine readily available screening test for the patient without any history to suggest the likelihood of an anaphylactic reaction the usual treatment strength suspension of procaine penicillin 300 000 units per ml may be used for the scratch test but *not* for an intracutaneous test This concentration should not be used where penicillin sensitivity already exists or is suspected In doing the scratch test the addition of a drop of water prevents too rapid drying of the heavy suspension The reaction should not be read earlier than fifteen minutes

Recent observations[47] confirm the value of this preliminary *scratch test but emphasize the additional value of a conjunctival* test employing a drop of the same aqueous procaine penicillin suspension In some instances only one of these tests may be positive It is the opinion of the author that the conjunctival test is more safely carried out *after* the scratch test has proved negative rather than simultaneously even though time is lost for as already reported[49] both a severe local ocular reaction and a generalized anaphylactic response may occur from absorption from the conjunctival membrane It must be stressed again that a negative test is no guar

antee against anaphylaxis In cases where there are indications of possible anaphylactic sensitivity both the scratch and conjunctival tests are most safely carried out with graded dilutions of penicillin ranging from 100 units per ml to 50 000 units per ml and preferably employing crystalline penicillin G solution Should these tests prove negative they may be supplemented by intracutaneous tests in graded concentrations and preliminary trial subcutaneous injections in ascending dosage

In anaphylaxis epinephrine subcutaneously 0 5 to 1 0 ml repeatedly remains the most effective antidote In extreme urgency it may be given intravenously A tourniquet should if possible be applied proximal to the penicillin injection site to delay absorption *The patient is placed in the recumbent position if this has not already been assumed spontaneously* It may be necessary to give at*tention to the maintainence of a free air way and oxygen may be* urgently needed Parenteral antihistamine is additionally useful *Corticotrophin or hydrocortisone intravenously may also be admin*istered but should not be depended upon as the major antianaphylactic agent *In protracted shock more powerful vasoconstrictor* remedies should be used such as levo arterenol by intravenous drip *It is probably superfluous to point out that shock reactions to peni*cillin can be a most critical emergency demanding the most prompt *and vigorous treatment More detailed discussion of this subject is* to be found in Chap 61

Therapy of the more usual forms of penicillin allergy is fairly well standardized with antihistamines orally and parenterally ephed*rine epinephrine in slow acting form and analgesics and antipy*retics for fever and joint pains as the first line of defense In the *more intense or persistent reactions resort may be had to steroids* or corticotrophin Where the manifestations are of the more severe *accelerated Type II or of the hyperergic Type III variety* intravenous corticotrophin or hydrocortisone can usually be relied upon *to induce a more prompt remission It may be wise when hyperergic* reactions have occurred to maintain steroid control for some time *with the purpose of preventing relapse of a dangerous form of tissue* reaction

Recent reports suggest that penicillinase an enzyme which hydrolyses penicillin to penicilloic acid may prove a useful new approach *in the treatment of penicillin allergy It does not displace those anti*allergic agents which control the body s response to the allergen but acts *by destroying the allergen itself*[49, 50] *It is administered intra*muscularly in a dose of 800 000 units which may be repeated in *three days* While it may also be given *intravenously it is then more*

likely to induce a chill and fever The precise efficacy of penicillinase in penicillin allergy awaits more extended observation A possible drawback may be its own potential capacity as a sensitizer [51, 59] Penicillinase has no place in the emergency treatment of penicillin anaphylaxis

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Febrile reactions and local induration with nodule formation at the site of inoculation are most commonly seen Rarely more serious sequelae are observed and of these neurologic complications such as convulsions are a frequent subject in recent reports A serious outlook with prospect of possible irreversible damage is pictured by Byers and Moll Toomey[3] Kong[4] and Escardo and Nazquez[5] How

TABLE 36 ANTIGENS AND HAPTENS CONTAINED IN PREPARATIONS USED FOR ACTIVE IMMUNIZATION

Bacterial vaccines	Viral and rickettsial vaccines
Somatic antigens related to immunity	Somatic antigens
Bacterial protein	Viral or rickettsial proteins
Endotoxins	Toxins
Exotoxins	
Toxoids	Antigens derived from host
Polysaccharides	Chick embryo culture
Lipoids	Egg white
	Egg yolk
Antigens and haptens unrelated to immunity	Membrane tissue and fluids
	Chick embryo tissue
Culture media	Tissue culture
Peptone (Witte Barna)	Cerebrospinal nervous tissue of host animal
Proteose	
Traces of horse serum	Red cells of host animal
Inactivators	Kidney tissue of monkey or human being
Formalin	
Phenol	Trace of horse serum
	Inactivators
	Preservatives etc
	Penicillin
	Streptomycin
	Polymyxin
	Neomycin
	Mercurial antiseptics
	Parahydroxybenzoate derivatives
	Phenol red or other indicators

ever with suitable precaution Melin[6] satisfactorily immunized 45 children with convulsive disorders This problem is also discussed in an editorial in the *Journal of Pediatrics*

An unusual instance of generalized purpura with angioneurotic edema reported by Freud and Greenberg[8] followed twenty four hours after the initial injection of a pertussis vaccine Five months and again one year later an intradermal injection of 0 1 ml of the

vaccine caused wheal formation with pseudopodia Challenge doses of 1 and 2 ml of the vaccine given subcutaneously at this time caused no reappearance of the purpura but reddening and induration of the site of injection were noted for twelve hours

Typhoid

Recent reports have raised the question of the efficacy of triple typhoid immunization[9, 10] While there is no doubt that high sanitary standards are of paramount importance in reducing the incidence of infection the need for proper immunization may paradoxically be even greater now in view of the restless migrations to distant lands With an ever decreasing reservoir of subclinical contact infection booster injections should be made a routine program

Apart from the usual local reactions with swelling tenderness erythema induration and systemic symptoms of fever sometimes accompanied by chills headache and general malaise the typhoid vaccine injection may rarely induce severe shock The injection if given intravenously will infrequently cause a fatal reaction[11] Occasionally neurologic complications similar to those seen in clinical infection with typhoid bacilli are observed after vaccination Bannwarth[12] attributed such reactions accompanied by increased protein in the cerebrospinal fluid to an allergic or parallergic mechanism Similarly Juon[13] reported that previously existing erythema nodosum erythema exudativum multiform eczema and alopecia areata may be reactivated by the vaccine injection Rossle[14] attempting to influence a favorable outcome in the course of typhoid infection by injection of typhoid vaccine noted the occurrence of hemorrhages in the sites of the typhoid process in the intestines mesentery spleen and cerebral meninges He indicated that these effects were not merely the result of added toxin but rather that they represented a pathergic phenomenon

Catarrhal Vaccines

Vaccines cultured from the respiratory tract are probably the most frequently employed bacterial antigens given for active immunization It is not the purpose of this discussion to enter into the relative value of this type of therapy It is sufficient to point out that both stock and autogenous vaccines have their protagonists

Reactions to these vaccines may be local delayed inflammatory in character or general accompanied by fever and malaise such as usually follow absorption of larger doses of bacterial products

In individuals sensitive to bacteria derived from the respiratory tract an allergic reaction in the nature of exacerbation of respira

tory allergic symptoms may ensue as in perennial rhinitis or asthma [1] Evidence of focal flare up of sites of previous injections or in areas of inflammatory disease support the concept of allergic re activity to bacteria or may also be explained as a mechanism similar to the Schwartzman phenomenon Bacterial sensitization may have a role in collagen disease reactions and vascular allergy [16] The use of catarrhal vaccines where such conditions exist should be tempered with caution

BCG

No ill effects attributable to allergy have been reported following BCG (bacillus Calmette Guerin) vaccination Localized induration with possible ulceration at the site of vaccination may be accom panied by swelling and tenderness of the regional lymph nodes It is believed that with the development of tuberculin hypersensitivity a state of increased resistance to natural infection is effected

Reactions to Toxoid Preparations

Reactions may occur not only to bacteria but also to their prod ucts such as toxins Toxoid preparations which are modified toxins are in common use Those of scarlatina diphtheria and tetanus merit special consideration

Toxoid preparations in addition to containing toxoid protein appreciable amounts of proteoses peptones and formalin are known to provoke allergic reactions which may be particularly se vere in the older age groups In such individuals a skin test with diluted vaccine using from 0 02 to 0 05 ml of a 1 10 to 1 20 dilution as in the Moloney [17] test with diptheria toxoid will elicit either im mediate wheal and flare reactions or local induration over a twelve to twenty four hour period and may serve as a guide in planning a course of vaccination

Scarlatina Toxoid Wang [18] reported two anaphylactic reactions among 100 persons vaccinated with scarlatina toxoid He indicated that prior Dick tests on these individuals may have been a predis posing factor inducing sensitization to the toxin

A fatal result in a naval cadet following the first streptococcus toxin injection (500 skin test doses) was reported by O D Brown field [19]

Diphtheria Toxoid Experience with primary and supplementary toxoid injections of diphtheria toxoid in over eleven thousand school children in New York City resulted in no alarming reac tions [1] Not more than three to four in a thousand suffered mild

local or general reactions such as fever while only one instance of a generalized rash was reported

An interesting experiment with a novel method of immunization was performed with adult volunteers exposed to nebulized aerosols of diphtheria toxoid Inhalation for fifty minutes resulted in appreciable rises or antitoxin blood titers with no ill effects However the second inhalation treatment produced tightness of the chest cough and headache attributed to allergy [1]

Schick Test Reactions following the Schick test and ascribed to the Witte s peptone contained in the preparation include acute anaphylaxis [4] which according to Beck occurred in three instances in over fifteen thousand Schick tests performed

Tetanus Toxoid In 61 042 patients given two doses of tetanus toxoid at an interval of six weeks Wittingham [6] described 2 acute anaphylactic reactions and 12 mild reactions such as urticaria headache and joint pain Others [7 31] have reported similar allergic experiences proved in some instances by skin tests and passive transfer studies to have been caused by the meat infusion products (peptone) Pruritic papular eruptions and angioedema may be similar to those encountered in allergy to foods [3]

ALLERGY TO VIRAL AND RICKETTSIAL VACCINES

With improved culture technics viruses and rickettsiae have become available to the immunologist for practical application These organisms acting as obligate parasites must be grown on suitable animal tissues In general two types of vaccines are used attenuated live virus vaccines as in smallpox rabies and yellow fever and killed virus vaccines derived from chick embryo or tissue culture

The introduction of the foreign substances present therein as well as those in their culture media have resulted in reactions of hypersensitivity

Allergy to Egg (Chick Embryo) propagated Vaccines

Antigenicity of the embryonic fluids and chick embryo proteins as indicated in animal experimentation and experiences in veterinary practice has been reviewed by Untracht and Ratner [33]

The experiences with animal immunization have been closely paralleled in human beings Reactions fall into the two general categories previously described and tabulated in Table 35

Reactions to vaccines of this type which are in common use are discussed below

Yellow Fever A form of allergic manifestation namely serum sickness-like reaction has been reported by Sulzberger and Asher[34] following the use of this vaccine In two individuals symptoms which appeared six and seven days after the injection included head ache pain in the joints nausea and vomiting together with an urticarial and erythema multiform eruption Symptoms in a third individual were similar but appeared after thirty six hours

Swartz[3] and Sprague and Barnard,[36] using this vaccine reported severe anaphylactic shock in egg sensitive individuals Skin tests and passive transfer studies demonstrated the presence of egg and chick protein antibodies Yellow fever vaccine is prepared from whole chick embryo

Typhus Vaccine That the yolk of the fertile egg may contain specific allergens is attested to by Park[37] who described a patient with a life history of egg allergy who had received an inoculation of yellow fever vaccine with no ill effects but collapsed with asthmatic breathing generalized urticaria and vomiting of blood and passed into a coma in fifteen minutes after an injection of typhus vaccine given about a year later He was shown to be sensitive to yolk al lergen

Other reports of severe shock reactions from typhus vaccine have been reported by Rubin[38] Roth[39] Plotz[40] and Sprague and Bar nard[36] Rubin was also able to demonstrate antibodies to egg yolk allergen His patient could tolerate hard boiled egg white but vom ited when whole egg was eaten indicating specific sensitization to egg yolk

Fatal reactions to typhus vaccine injection have been reported by Plotz[40] Rifkin[41] and Walker[4] In each instance a history of egg in tolerance could have been elicited had the question been posed Autopsy in each instance revealed the typical anaphylactic lung of the guinea pig type

Rocky Mountain Spotted Fever This vaccine produced from chick embryo culture may also cause typical anaphylaxis Caution in its administration as with other vaccines of this group is indi cated since Forman[43] has described a fatal reaction occurring in a child after administration of the vaccine

Influenza Virus Vaccine Detailed studies of the reactions encoun tered in allergic and nonallergic children have been reported by Ratner and Untracht[44–47] The incidence of individuals in whom egg sensitivity may be of an order high enough to present serious hazard from injection of chick egg-propagated vaccine is estimated to be about 1 or 2 in 1 000 treated persons In these a history of egg in tolerance is found frequently enough to caution the physician In

each instance of suspected egg intolerance an intradermal test with 0 02 ml of the undiluted vaccine should be done prior to inoculation Should a systemic reaction occur while testing an exquisitely egg sensitive individual an immunizing dose should not be given However with a moderately positive reaction (moderate wheal with flare) repeated cautious intradermal injections of small doses (0 1 ml) together with small amounts of epinephrine (0 1 ml of 1 1000 solution) can provide effective immunization without reactions

In studies conducted over a three year period children who had received as many as 30 separate injections of influenza and mumps virus vaccine nevertheless failed to develop intolerance to egg It would seem that with this ubiquitous food a hard core of resistance to sensitization is maintained from daily contact in the diet

That inoculation of influenza virus vaccine may have serious consequence is attested to by reports of fatal reactions [4, 48] Salk [49] believed that the death in one of these instances which occurred in a three and one half year old child was caused by viral toxins in the vaccine resulting in a necrotic type of pneumonitis resembling the Schwartzman phenomenon This example presents a dramatic plea for low dosage intradermal immunization in children and perhaps too in debilitated or aged individuals

In view of the Asian influenza epidemic of 1957 special attention is given to the use of the vaccine available for this type of influenza It should be pointed out that the virus involved here is akin to the A virus of influenza although it differs from it antigenically All the principles concerning prophylaxis for influenza previously described are therefore applicable to the so called Asian influenza Some experience has already been obtained with the use of a vaccine specific for this type of influenza In evaluating the prophylactic experience the United States Public Health Service has recommended that the concentration of the vaccine be increased from 200 to 400 chicken cell agglutination units per milliliter It is believed that the antibody production is adequate in 95 per cent of persons treated with this higher concentration In allergic and debilitated patients smaller and more frequent injections (0 1 ml) given intradermally can be effective without causing undue reactions as encountered with the large doses (1 0 ml) administered intramuscularly

Other vaccines of the chick egg culture type which have not yet found general application are equine encephalomyelitis mumps and herpes simplex Allergy to these agents consisting mainly of local manifestations has been discussed in recent reports [50-54]

Animal Propagated Vaccines

Antirabic Vaccine Because of the affinity the viral agent has for the cerebrospinal nervous system this vaccine presents antigen specificity characteristic of both the host animal and the organ in which it is grown Thus it is not surprising that many reports are found describing neurologic sequelae following the use of this vaccine

The occurrence of acute myelitis with fatal outcome following antirabic vaccine injection has been described by Ansell[55] He quoted Greenwood s estimate of the incidence of such neuroparalytic accidents as 1 in 8 517 cases (0 012 per cent) treated with killed phenol vaccine and 1 in 5 814 cases (0 017 per cent) for all types of antirabic vaccine the mortality in each group being 25 per cent The cause of the neurologic involvements may be viral infection toxicity or allergy[56, 57]

The incidence of neuroparalytic accidents of rabies vaccination was further estimated by McFadzean and Choa[58] who reviewed records of 14 119 patients in Hong Kong during the years 1919 to 1952 With the injection of Semple vaccine 17 cases of paralysis occurred an incidence of 1 in 831

Some indication of impending adverse reaction may be gleaned from the advent of urticarial rash and increasingly severe local reactions at the injected sites[59] A positive skin test with diluted vaccine occurs in every person who has had a neurologic reaction and in 60 per cent of all individuals vaccinated[60]

Smallpox Attenuated in passage through the cow this classic vaccine with live virus has a record of effective immunization unsurpassed by any other single vaccination procedure Complications in this type of immunization are similar to those which occur in the course of natural infection and allergic manifestations are in every respect comparable with those of the more common exanthemata

Encephalitis following smallpox vaccination requires an incubation period Finley[61] noting the similarity of this with the incubation period prior to the onset of the exanthema of measles ascribed an allergic mechanism to both phenomena

Smallpox vaccination may be followed by exanthems of erythema urticaria or purpura[6, 63]

Tissue cultured Viral Vaccines

The tissue-culture method offers possibilities for new vaccines which in the coming years will perhaps encompass the entire field of viral diseases[64] An outstanding example is the Salk poliomyelitis vaccine A recent addition is the adenoviral (APC) vaccine

Such vaccines may retain antigens of the host tissue That traces of monkey kidney protein may be sufficient to induce allergic reaction in a rare case is suggested by Crepea[65] His patient a nine year old boy with a history of sensitivity to monkey on contact in the zoo reacted to each dose of Salk polio vaccine with asthma and rhinitis within a few hours Scratch tests with diluted vaccine (1 10) elicited a characteristic wheal reaction This child tolerated penicillin orally

Such reactions as have been reported with the Salk vaccine are relatively mild and consist mainly of urticarial and other rashes in rare instances[66] [6] The fear of specific organ sensitization induced through the use of tissue-culture vaccines has largely been dispelled since no instances have been reported despite millions of injections given[68-70] (Crepea s[65] report is an exception Sensitivity to monkey tissue is strongly suggested but not proved since a skin test with monkey tissue extract was not performed)

In view of the widespread use of penicillin in the treatment of infection and the increasing incidence of anaphylactic reaction to this antibiotic McLean[71] wisely suggested substitution of another antibiotic such as polymyxin in the manufacture of the Salk poliomyelitis vaccine

GENERAL CONSIDERATIONS IN THE PROPER USE OF VACCINES

Whenever a vaccine is administered thought should be given to the possibility of reactions The following precautions should be followed

In the presence of infections accompanied by general malaise or fever it is best to withhold routine elective immunizations since febrile reactions are inevitable in some proportion of inoculations and at times may be unpredictable The physician must always be cognizant of calculated risk to the patient which is to be weighed against benefits derived from immunization

Where cerebrospinal nervous system complications have been noted in prior history divided smaller doses of vaccine should be used

Toxoids should be given to adolescents and adults only after a preliminary intradermal injection of a small test dose (0 02 ml to 0 05 ml) using a 1 10 dilution

The route of administration plays an important role in the severity of allergic reactions Wherever possible the intradermal route with a small amount of antigen is to be preferred Alum precipitated vaccines are best given intramuscularly Subcutaneous inoculations

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Bela Schick | 49

SERUM SICKNESS AND SERUM SICKNESS-LIKE REACTIONS

Serum sickness provided the basis for studying the clinical observations pathogenesis and theory of allergy Pirquet's[1] observation of a change in the incubation time helped explain why the first injection of foreign protein creates an altered reactivity of the organism The reinjection of the same kind of foreign protein (in the original study this was horse serum) is followed by either an immediate or an accelerated reaction *The incubation time is missing or at least decidedly shortened to four to six days whereas the first injection is followed by symptoms only after eight to twelve days*

Pirquet coined the term *allergy* for this altered reactivity It must be added that this allergic reactivity is frequently characterized by an intensification of the regular symptoms The usual symptoms are urticaria (local or generalized) edema fever and lymph gland swelling Sometimes other kinds of skin eruptions—morbilli like rubeolar or erythematous—are seen

In an attempt to explain the pathogenesis of this disease Pirquet and Schick[2] evolved the theory that injected foreign protein cannot be tolerated by the human organism and must be destroyed in a similar way to that in the intestinal tract where digesting enzymes act as antibodies In the course of digestion toxic intermediary substances are created In the intestinal tract they rapidly progress to nontoxic amino acids and furthermore are detoxified by passing *through the intestinal wall and by the liver where the intrinsic protein of the organism is synthesized* When injected parenterally

such intermediary toxic substances can exert their effect because no detoxification takes place. The specific antibodies produced after injection of foreign protein interact with the foreign protein and this interaction is the cause of the symptoms of serum sickness. The formation of specific antibodies can be demonstrated by the appearance of precipitin. However, we purposely avoided identifying these antibodies as being responsible for the symptoms of serum sickness.

I wish to emphasize the dangers of this form of allergy. It persists for a long time, even for life, and leads to hypersensitivity and not to immunity. It can cause fatal anaphylactic shock. Therefore I propose to call this allergy to foreign protein a *pathologic* form of allergy. We pointed out that Nature was not prepared to handle parenterally injected foreign protein. The human organism had to develop a strong defense against the invasion of pathogenic microorganisms which produce infectious diseases. The mechanism of allergy is extremely effective against this form of attack and leads to immunity.

The first attack of an infectious agent is on an organism which has no bacteriolytic or antitoxic antibodies against the invading microorganism. An incubation time of eight to twelve days is needed to mobilize the antibodies. Therefore, during this period the invading germ can multiply without interference and a large amount of toxic substances can accumulate. The mobilized antibodies will terminate the multiplication and kill the invading germ. In case of reexposure the now present antibody can go into action *without any* or with a shortened incubation time. This mechanism will protect the organism against disease by making it immune. This *physiologic* form of allergy is very beneficial, whereas the allergy against foreign protein substances is a pathologic form which does not lead to immunity. It is the latter type of allergy which is treated by the allergist.

An important and interesting achievement in allergy was Landsteiner's discovery [2] that very simple chemical substances are able to produce symptoms of allergy by combining with the protein of the organism and thus becoming foreign proteins. Such substances are called haptens. They stimulate the production of specific antibodies. Through the interaction between antigen and antibody a reaction ensues which is similar to that of a foreign protein.

Schick and Sobotka [3] demonstrated that the use of nirvanol in treating chorea produced morbillous rashes and fever after an interval of eight to ten days. This reaction, which resembled a form of serum sickness, ameliorated the intensity of the choreatic movement. We found this "chemical" allergy to be of particular interest because

we were able to establish that the commercial preparation of nirvanol was really composed of two forms one levorotatory and the other dextrorotatory A nirvanol tablet contains 50 per cent of each form The most striking discovery was that the levorotatory form was biologically potent and responsible for the nirvanol sickness and for the beneficial effect on chorea while the dextrorotatory form was relatively inactive

In an unpublished study of over 100 cases of nirvanol sickness Spiegel and Schick found that this chemical allergy was somewhat different from serum sickness in that it was of shorter duration Several months after the nirvanol treatment the immediate or accelerated reactivity was found to have disappeared and normal reactivity was reestablished We concluded that in the case of nirvanol sickness the antibodies were lost earlier than in serum sickness and no lasting impression was left on the cells of the organism In its persistence nirvanol allergy in human beings stands between serum allergy of the rabbit and of the guinea pig

After considering the findings of Landsteiner and others as well as our own it was not surprising to find that chemical substances having no relation to horse serum or other proteins could produce a specific allergy Therefore it was to be expected that allergic symptoms might follow the repeated administration of antibiotics Indeed after the introduction of the antibiotics there were reports of allergic and even hyperergic (anaphylactic) features following the injection or oral administration of penicillin streptomycin and other antibiotics The same explanation as that for allergy to Landsteiner's compounds and nirvanol is applicable

I had a very early opportunity to observe typical symptoms of serum sickness after injections of penicillin My first observation was reported in a paper entitled Joint Allergy [4,5] given at the allergy meeting in Philadelphia in 1947 An eight year old boy was operated on by Dr Touroff for a patent ductus arteriosus Two days after the successful operation the left lung became congested and fever to 104 F developed To combat the pneumonic infiltration 100 000 units of penicillin were administered intramuscularly daily for four days The effect of penicillin was very satisfactory The temperature became normal and the lungs cleared The patient was discharged Eight days later a severe generalized urticarial eruption appeared accompanied by high temperature and very annoying itching The itching was so intense that the patient was unable to sleep Edematous swelling of both wrists and ankles developed and all finger joints became very painful and swollen The pain was intolerable necessitating administration of morphine The patient could not bend

his fingers and was unable to make a fist Fever ranged between 101 and 103 F Benadryl somewhat controlled the urticaria and itching but not the pain The condition lasted three days with slowly diminishing intensity

The severity of the symptoms reminded me of how tetanus antitoxin frequently produces more intense and painful symptoms than other antitoxic serums It is very difficult to understand why it is that only tetanus antitoxin has such an unpleasant effect I discussed this problem with Dr William H Park and inquired whether any difference exists in the preparation of tetanus and diphtheria antitoxin Dr Park stated that the same method was used in the manufacture of both It must be assumed therefore that protein substances in the tetanus bacillus itself are responsible for the difference in the intensity of the symptoms

Since penicillin and streptomycin are the most frequently used antibiotics it naturally follows that allergic symptoms are seen more often after the use of these drugs particularly penicillin Some fatalities have been reported after penicillin injections although it seems that the danger of extreme hyperergic (anaphylactic) reactions is not great Intravenous injection should be avoided if allergy to penicillin or streptomycin exists Whether allergic patients are more frequently allergic to antibiotics is not known However I would advise caution and the taking of a detailed history concerning known sensitivity before making the injection Some patients are decidedly allergic to penicillin and rapidly develop severe edema of the face even after oral administration In such patients the antibiotics should certainly be selected with great care Fortunately many new effective antibiotics are available If allergic symptoms appear it is preferable to replace the offending antibiotic drug with another The treatment of these symptoms is the same as in serum sickness Benadryl Pyribenzamine epinephrine and cortisone may be used

Many physicians use antibiotics without hesitation even when less intensive treatment such as bed rest aspirin etc would be sufficient to control the annoying symptoms of simple colds or other mild upper respiratory infections Several years ago I asked a prominent physician from Los Angeles whether he brought anything new from California His answer was that they had just discovered that sore throat could be treated with aspirin

For related discussion see Chaps 46 47 61

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For related discussion see Chaps 46 47 61

should be performed although the results do not always predict what will occur when serum is administered Laurent and Parish[1] state that intradermal conjunctival and scratch tests for the detection of serum sensitivity are unreliable The small trial dose given subcutaneously is preferable It seems to me that even if one wishes to use the subcutaneous trial dose it would be better first to perform the usual tests and eliminate those individuals considered too sensitive to receive horse serum especially since bovine TAT to which many fewer persons are sensitive is available

Intradermal and conjunctival tests must be performed correctly before any conclusions can be drawn from the results It is advisable to use 1 100 and then 1 10 dilutions for the intradermal tests[14, 33] Undiluted serum or more than 0 02 ml should never be used for this test[11, 14] for severe constitutional reactions as well as too many false positive tests may result[33, 34] In 1928 Spicer[35] tested 353 patients and found no positive ophthalmic tests with a 1 10 dilution but found several positives with a 1 1 dilution or concentrated normal horse serum She stated that in her opinion the best indicator of clinical sensitivity is the ophthalmic test with undiluted serum Claiborn[36] in 1932 came to the same conclusion after testing 465 patients Tuft[14] also recommends undiluted serum for this test The author tested 74 allergic individuals by the conjunctival method with 1 10 dilution and with concentrated normal horse serum[37] One subject reacted questionably to both strengths one was definitely positive to both and one was negative to the weaker but positive to the stronger All these experiences indicate that undiluted serum should be employed if the 1 10 dilution is negative

In interpreting the intradermal tests with horse serum it is generally agreed that a slight to moderate reaction (1 to 2 plus) is clinically unimportant[34] However a strong reaction (3 to 4 plus) especially to the weaker solution is a definite danger signal but it may not be a contraindication to the use of TAT depending on the history and the result of the conjunctival test When the ophthalmic test is negative the danger of a serious serum reaction is very slight[34] A positive ophthalmic test rarely if ever occurs when the intradermal test is negative[14, 3, 3] A positive eye test is an absolute contraindication to the administration of horse serum[10, 11, 8, 31, 35-4] The methods of testing and the interpretation of results as well as the procedure and precautions described below apply not only to equine TAT but equally to all other kinds of antiserums including bovine TAT

The possibility of desensitizing by gradually increasing taneous injections of serum has been seriously questioned[1]

(NOTE A positive eye test can be counteracted by one or two drops of 1 1 000 epinephrine in the conjunctival sac)

Procedure

History and Tests	What to Do
1 History of horse sensitivity (asthma nasal or ocular symptoms itching edema etc) from contact with horses History of serum reaction immediate or within three days	1 *Do not test with or give horse serum* Substitute Bovine TAT Lyovac (Sharpe & Dohme) and do preliminary testing as with horse serum
2 Skin and eye tests positive	2 *Do not give horse serum* Use bovine TAT
3 Skin test strongly positive (3 to 4 plus) and eye test negative	3 Give bovine TAT If necessary to use horse serum desensitize If eye test is not feasible do not give horse serum
4 Skin test negative or slightly positive (1 to 2 plus) and eye test negative Positive history of allergy or previous serum administration	4 Give 0 1 ml TAT subcutaneously If no reaction occurs after twenty minutes give remainder intramuscularly If eye test is not feasible give first injection of 0 1 ml 1 10 dilution
5 Skin test negative or slightly positive (1 to 2 plus) and eye test negative No history of allergy and no previous serum administration	5 Give TAT in one dose intramuscularly If eye test is not feasible give preliminary 0 1 ml TAT subcutaneously

Additional Precautions

1 It is dangerous to repeat serum administration one week to three months after the last dose but *if necessary* it may be given with great care

2 When giving serum always aspirate before injecting Have epinephrine sterile syringe and tourniquet ready from the beginning of testing until the patient leaves

3 Always have patient wait thirty minutes after administration of serum If signs of generalized allergic reaction appear treat vigorously with epinephrine etc (see Chap 61)

4 In case of anaphylactic shock within seconds minutes or hours after injection (symptoms apprehension sweating flush itching

urticaria angioedema sneezing nausea vomiting coughing tightness in chest wheezing asthma cyanosis lumbar pain drop in blood pressure tachycardia collapse coma and convulsions) treat with (1) tourniquet above site of serum injection (2) epinephrine (0 5 to 1 ml intramuscularly or intravenously) repeated as needed (3) antihistamines but not instead of epinephrine and (4) artificial respiration and oxygen if needed Later for continued shock give infusions of levartenol and ACTH

5 If in doubt about administration of serum admit the patient to a hospital

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PART FOUR

ALLERGY IN CHILDHOOD AND OLD AGE

M Murray Peshkin

51

ALLERGY IN CHILDHOOD

At least 10 per cent of the population of this country or 16 500 000 persons suffer from some form of allergy in need of treatment Of the chronic diseases in this country allergy ranks third in prevalence with heart disease and mental illness taking the first two positions There are 50 500 000 children up to fifteen years of age 5 000 000 of whom have allergy and at least 2 500 000 of whom have asthma and hay fever Thus allergy is a common American ailment and it is the practitioner s responsibility to diagnose it early and to treat it intelligently

DIAGNOSTIC SENSITIZATION TESTS AND THE HISTORY

With the introduction of allergy tests about forty years ago as a means of determining the etiologic factors of certain entities now recognized as allergic disease the clinical approach to the study and treatment of these diseases was placed on a rational basis After the completion of a thorough history and physical examination a clinical diagnosis is made and the physician then proceeds to search for the cause (etiologic diagnosis)

The first and one of the most important steps in determining the causal factors of allergy is the history of the patient s ailment The form of therapy to be instituted may be indicated by the history which also may show whether a positive skin reaction to an allergen plays a role The history may show that a patient is sensitive to a given substance despite the fact that the skin test reaction is nega

tive.[1] Family history aids in determining the presence of an allergic constitution.

Testing with allergens can be done at any age. A positive reaction, especially with the intradermal technic, may cause immediate and alarming symptoms of shock, such as asthma, urticaria, angioedema, intestinal colic, vasomotor collapse and even death. For the pediatrician and general practitioner who should use only one method of testing, the method of choice is the scratch test. A person with a negative skin reaction to an allergen who has active clinical symptoms from that allergen is called a negative reactor. Negative reactors who have been treated with pollen or other inhalant extracts with the average dose at the upper limit usually used for the positive skin reaction patients may fail to be relieved of their symptoms. Large doses of specific allergenic extracts are needsd for effective treatment of the skin refractory cases.

Sensitizations are usually multiple and are more frequently encountered in children than in adults. Food sensitization with test allergens is discovered more readily in children than in adults. Often the offending food has to be determined by test diet when the skin test is negative.

The size or intensity of a positive reaction to an allergen does not determine its importance in the etiology, nor does it indicate the degree of general (systemic) sensitivity present.

TREATMENT

The ideal treatment is the separation of the patient from the offending substance. From a practical standpoint this is not always possible. The simplest procedure is to desensitize (hyposensitize) the patient so that his tolerance to the inhalant allergens is increased. The principles of bacterial immunity apply to the desensitization of persons with hay fever, asthma and other allergies due to nonliving substances, but there is not the rapid and dramatically effective prophylactic response observed with bacterial vaccines such as diphtheria and tetanus (see Chap. 56).

Food sensitivity in children is a relatively simple problem. The offending food is removed from the diet for a period of at least one to two years. This sensitivity tends to disappear spontaneously and for this reason desensitization treatment is not employed.

Specific desensitization treatment with extracts of causal allergens is effective in a majority of children. Often additional therapeutic agents termed nonspecific are employed, especially in the treatment of asthma. It should be borne in mind that nonspecific therapy

(injections of mixed stock bacterial vaccines milk blood or snake venom) at best is merely a palliative measure that offers a temporary relief from symptoms for varying periods of time Many types of nonspecific treatment employed for adults particularly those inducing fever and shock cannot be safely applied to children

The removal of tonsils and adenoids does not relieve asthma except in a few instances and then the relief is only temporary The indications for adenotonsillectomy are the same for allergic and nonallergic children It is wise however to warn the parents that the operation will not relieve the asthmatic condition and may even aggravate it for a time[3] Elective operations should not be performed during the pollen seasons

The injection of allergenic extracts during the poliomyelitis season in not contraindicted[4]

The antihistaminic drugs are being used widely and relatively effectively for the relief of hay fever perennial allergic rhinitis certain types of urticaria and angioedema In my experience antihistamines in adequate doses are also indicated for asthma in infants without respiratory infection Unfortunately these drugs continue to be commonly used for asthma in older children despite their ineffectiveness It is now realized that the antihistamines have their limitations in hay fever and moreover *do not* desensitize the patient against the offending pollen In the absence of pollen desensitization antihistaminic drugs are not without risk for they may predispose to asthma (see Chap 58)

The steroid hormones do not cure allergy nor do they have any influence on the immune mechanism However at times they may be lifesaving and as adjunctive agents have a definite place in the management of the allergies provided their limitations and harmful effects are clearly understood and respected The routine use of steroids for the common allergies to the exclusion of determining the causal allergens and specific desensitization is to be condemned (see Chaps 34 and 57)

The role of the common specific allergic syndromes may now be evaluated

BRONCHIAL ASTHMA

Asthma is the most common major allergy of childhood Asthma may be broadly defined as a recurring paroxysmal dyspnea more marked in expiration associated with wheezing When an attack of asthma persists for more than forty eight hours in spite of repeated injections of epinephrine hydrochloride as well as other drugs the attack is referred to as *status asthmaticus* When asthma is protracted

and remains severe over a long period of time despite appropriate modern treatment it is referred to as intractable

The younger the patient and the sooner specific allergic treatment is begun the better are the prospects for controlling the asthmatic condition and enabling the asthmatic child to lead a normal useful and happy life Parents should never neglect treatment no matter how lengthy Yet too many physicians continue to advise parents against allergy investigation and treatment because the child will outgrow the asthma As a result many children are consigned to the fate of merely waiting to outgrow their affliction Replacing early appropriate treatment with that of waiting and hoping leads to the danger of serious chronic complications and considerably diminishes the chances of ultimate relief There are no statistical data available in the literature or elsewhere indicating that children *outgrow their asthma Often the apparent outgrowing of* asthma is due to accidental removal of an allergen or changed environment Reexposure to an allergen or acquisition of another inhalant sensitiveness during adult life frequently causes a recurrence of the asthma About 80 per cent of children respond favorably to allergy treatment

Psychogenic Factors Emotional disturbances may play an important and distressing role in allergic disease especially asthma but I have yet to find a single case of asthma caused primarily by a psychophysiologic disorder and asthma has not been experimentally induced on that basis The role of psychophysiologic disturbance in chronic disease is easily understood Children with chronic asthma who fail to respond to appropriate modern treatment in their own community must be treated sympathetically About 10 per cent of all asthmatic children are in this group[5] They account for the highest incidence of deformity of the chest chronic bronchitis emphysema retarded growth and undernourishment among other physical complications These children are the intractable asthmatics pulmonary cripples We have learned that this type of child often holds on to his crippling illness for reasons related largely to his human rather than his physical environment These children manifest various personality disorders Thus the destructive effects of intractable asthma include the social and psychologic deterioration not only of the child but also of his family his human environment

Experience has amply demonstrated that successful alleviation of the child s emotional disturbance is invariably doomed to failure while he resides in his own home even when psychiatric treatment is available for both child and parents A child struggling continually

for air is cyanotic and fatigued and is hardly a subject whose interest or attention could be diverted from himself. Even gentle psychologic treatment of such a gravely sick child may intensify the asthma. The humane and most dependable therapeutic measure to break effectively the vicious circle of physical and emotional suffering in a child with intractable asthma is "parentectomy"* : removal of the child from his human environment to a new home where a warm emotional climate is provided by sympathetic mother and father figures.[6, 7] Here relief from asthma, sometimes occurring dramatically within a few hours or days, gives the child courage to take a new lease on life. Here his personality emerges and develops slowly into mature ways. There are only a few institutions in this country where this type of child may receive medical, psychologic, sociologic, educational and domiciliary care (see Appendix IV).

It is difficult to isolate the specific benefit produced by a change from the environment of the home to the environment of an institution specializing in the care of intractable asthmatic children. The allergist undoubtedly might think of changes in the nature of exposure to allergens, the sociologist would consider changes in the social environment, and the psychologist would stress the effect of separation from the parent. There is no doubt that certain parents can be threatening to their children. In certain instances separation from the parents may be a very realistic technic because it removes threatening factors from the psychologic life of the child. Abramson[8] points out that many parents do not reject their children but threaten them by an engulfing type of domination. It might be well to reemphasize that "parentectomy" by no means implies that psychologic factors are a primary process in the causation of immunologically allergic disease in childhood. "Parentectomy" for the intractable asthmatic child, however, does remove many threatening

* EDITORS' NOTE.—The authors' discussion of "parentectomy" does not reflect the opinion of the editors. To us parental separation as a change in the human environment is drastic and tantamount psychologically to parental rejection. It is very possible that the benefits gained are those due to change from home environmental allergens, separation from bacterial contacts (carriers), and diet and climatic changes. Acceptance of the desirability of "parentectomy" would imply acceptance of psychologic factors as the major cause in the etiology of allergic disease in childhood. We believe that psychologic factors can be important but not necessarily the sole cause. Separation from parents may be helpful at times, but this should be temporary pending psychologic adjustment on the part of *both* parents and child. We dislike the term "parentectomy" because it implies complete and permanent severance—a sort of human surgery. Perhaps another term is indicated.

psychologic vectors which have become more important than the immunologic vectors. All of our studies at the institutional level since 1940 support this view.

Follow-up studies * on 150 children who have returned to their own homes after an average absence of two years revealed that 90 per cent remained well while away from home. One or more years after they returned to their own homes 80 per cent continued to be free from asthma or to have only an occasional spell of wheezing.[8] We have learned that parentectomy for the intractable asthmatic child can be successfully performed and is now acceptable as a rational procedure for the rehabilitation of the total child. We continue to learn more and more about this type of child but we have not yet uncovered the basic mechanism responsible for his recovery.

HAY FEVER

The incidence of pollen allergy in the United States and Canada is higher than it is in other countries largely because we have three distinct pollen seasons with the fall pollen particularly of the ragweed type possessing an index of sensitization higher than the pollens of trees (spring) or grasses (summer). Moreover the more toxic pollens of the fall season are almost exclusively limited to the North American continent.

The role of the psychologic factor in uncomplicated pollen allergy in children is minor probably because the degree and duration of suffering is considerably less than in children suffering from chronic asthma or allergic dermatoses of long duration. In all likelihood asthma occurs as a complication in from 40 to 60 per cent of the pollen sensitive children.

In uncomplicated cases avoidance of exposure to pollen is the ideal method of treatment but this is impossible for the majority of sufferers. Hence the injection of specific pollen antigens for purposes of desensitization assumes vast importance and continues to remain the treatment of choice. Pollen treatment should be repeated every year in order to maintain protection. In some children specific desensitization treatment may be inadequate if the physician fails to recognize the presence of sensitizations other than pollen. Frequently these nonpollen substances are tolerated through the year except at pollination time when they intensify hay fever and asthma symptoms.

It is estimated that with careful treatment from 70 to 85 per cent of the patients are markedly or entirely relieved of symptoms. It is desirable that the patient should have at least two seasons of com

* Dr Samuel Grosberg and Dr Howard G Rapaport assisted in the follow up studies

plete freedom from symptoms while he is being treated before treatment is discontinued The percentage of patients remaining permanently free from symptoms has not been satisfactorily determined at this time

Perennial Allergic Rhinitis This is one of the most common complications of allergy in childhood It is commonly associated with recurrent upper respiratory infections and it frequently precedes the onset of bronchial asthma with which it is almost always associated The causal allergens of allergic rhinitis are the same as those involved in bronchial asthma and positive response to treatment may be difficult to obtain Polypoid degeneration of the turbinates is not uncommon while large obstructive polyps are relatively rare Most instances of sinus disease in children are essentially allergic in character

ALLERGIC DERMATOSES AND OTHER ALLERGIES

Eczema The most important skin disease of infancy and childhood is allergic eczema and its chronic counterpart neurodermatitis or chronic eczematous dermatitis [10-14] As the child grows older typical sequelae are recurrent upper respiratory infections hay fever and asthma (see Chap 30)

The causal allergens during infancy are largely foods later inhalant and contact substances must be considered The dietetic and local treatment of the skin condition is well defined (see Chaps 30 and 53) ACTH and cortisone derivatives should be used only for relatively short periods of time to control severe cases of atopic dermatitis or for exacerbations of the disease when all other measures fail (see Chap 34)

Urticaria and Angioedema These dermatoses are common in children but do not last so long and are not so troublesome as they often are in adults Urticaria in childhood is often due to foods such as fish eggs berries nuts and chocolate It may also be caused by drugs and serums and occasionally is a result of contact with eggs fish animal dander or silk Inhalant substances heat light and cold are other possible causes The treatment of these dermatoses is removal of the offending substance Occasionally hyposensitization is necessary when inhalant allergens cannot be avoided In about one third of the cases the cause is undetermined (see Chap 31)

Gastrointestinal Allergies These are essentially due to food or drug ingestion and rarely to inhalant substances (pollens) Depending on the tissue involved the allergic lesions may be in the mouth stomach or intestines and may provoke subjective and objective

symptoms such as nausea vomiting diarrhea constipation singultus pyrosis belching bleeding or syndrome complexes such as pyloro spasm gastroenterospasm (colic) simple or ulcerative colitis intus susception and celiac syndrome The treatment is essentially dietetic When pollen allergy is the cause hyposensitization treatment is ef fective (see Chap 41)

PROPHYLAXIS AGAINST ALLERGY

Although present day knowledge of the etiology diagnosis and treatment of allergic conditions in children affords a good back ground for the use of prophylaxis it is a much neglected area in allergy practice (see Chap 62)

It is generally recognized that allergy tends to run in families The tendency to inherit the allergic predisposition the soil or the physiochemical make up is conceded However a specific allergic disease is neither transmitted nor inherited Eugenic marriage may be an ideal measure but it it an impractical one Children with bi lateral inheritance of allergy are especially likely to develop allergic conditions Dieting during pregnancy has not been practical or appreciably efficacious in my experience Prophylactic measures ap plied to the children of allergic parents have been of value Nurs ing mothers should be given food in allergenically denatured form Evaporated milk or Mull Soy should be given to the newborn All foods should be cooked and denatured as much as is practical Vita mins should be chemically altered or of synthetic origin The periods of greatest vulnerability to sensitization appear to be infancy and early childhood and during illness and convalescence

Eczematous children should be protected from the sensitizing sub stances known to cause asthma and hay fever Early recognition and treatment of perennial allergic rhinitis hay fever and frequently recurring respiratory infections in children from an allergic family in most instances will prevent the major complication of asthma

Allergically predisposed children should be protected against the need for antiserums through active immunization with diphtheria and tetanus toxoids [15, 19] They should also be immunized against pertussis and poliomyelitis Booster doses of these vaccines should be given in accordance with accepted practice

Infected tonsils and adenoids should be removed as soon as pos sible but such an operation should be avoided during the pollen seasons

Prophylactic treatment should result in a considerable reduction in the incidence of allergic conditions particularly asthma Parents

as well as children must be properly prepared for acceptance of this infrequently practiced therapy The successful application of prophylaxis to allergic diseases in children requires patience and education

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Robert Chobot *

INFECTIOUS ASPECTS OF ASTHMA IN CHILDREN

The importance of infection as a causative factor in asthma in children cannot be overemphasized There are those who question whether infection causes asthma and whether infective asthma is allergy On the basis of clinical observation there is no doubt that upper respiratory infection results in attacks of asthma and patients *with such attacks do not differ in the slightest from* those having asthma from inhalants or foods The only question that is raised is whether infection can cause asthma After an acute upper respiratory infection a child may become dyspneic have a chest filled with asthmatic rales and present the clinical picture of asthma When the infection subsides the chest returns to normal From then on the child may be asthmatic whenever he has a recurrence of his upper respiratory infection It is noteworthy that when measures are taken to control the infection and to remove infected foci the child promptly begins to improve Any hesitance in the acceptance of this fact will interfere with proper therapy

The frequency with which asthma follows an acute upper respiratory infection in the allergic child has long been recognized The possibility that foci of chronic infection constantly feed bacterial toxins which are capable of producing asthma has not been universally accepted The primary argument of those who do not believe in infective asthma is the inability to obtain positive skin tests to

* Deceased

bacteria or to demonstrate the presence of skin sensitizing antibodies in the blood of these patients It is common knowledge however that clinical sensitivity to foods exists in the absence of positive skin tests and circulatory skin sensitizing antibodies Yet the absence of similar tests makes some hesitant to recognize bacteria as causative agents Fortunately medical opinion is coming to accept the existence of bacterial allergy

The asthmatic child can of course have his symptoms precipitated by inhalant substances and foods as well as by bacteria A history of personal and familial allergy is common in asthmatic children with a history of repetitive upper respiratory symptoms The physical findings are typical of those found in the child with asthma but the tonsils adenoids and paranasal sinuses are usually infected These children like those sensitive to the inhalants and foods have a positive familial history of allergy in over 50 per cent of the cases [1] Whether infection or any other allergen is the cause of asthma the constitutional capacity for sensitization is present as a result of hereditary transmission It is this capacity for sensitization that makes the child allergic irrespective of the nature of the specific precipitating causes In predisposing to infective asthma the childhood infections—measles pneumonia pertussis and scarlet fever—are of great importance These frequently start the syndrome and it is the secondary infection of the respiratory tract especially in measles and pertussis that causes the initial attack of asthma

The foci of infection in children are most often in the tonsils and adenoids The organisms usually involved are hemolytic streptococci pneumococci and hemolytic staphylococci A relatively high blood eosinophil count is a common finding A diagnosis of infective asthma is made largely by eliminating other possibilities The frequency of upper respiratory infections and the isolation of pure cultures of pathogenic organisms from suspicious foci of infection are of the greatest importance in diagnosing infective asthma especially when several examinations show the presence of the same pathogen When the removal of infected foci is followed by a marked improvement *the evidence is of course impressive*

In a study of 400 asthmatic children chronic focal infection was found to be the sole cause in 30 per cent of the cases Table 38 summarizes these findings and indicates the importance of focal infection both alone and in combination with other factors

The therapy consists of the treatment of acute infection with the usual antibiotics and the subsequent removal of the infected foci The importance of the early removal of infected tonsils and ade

noids cannot be overemphasized. Vaccine therapy is instituted subsequent to the removal of the infected foci. It is essential that care be exercised in the surgical removal since 50 per cent of the tonsillectomy patients seen have had previous tonsillectomies and recurrences. The diagnosis of recurrent adenoids should be made by direct examination or by lateral soft tissue roentgenogram of the nasopharynx which outlines adenoid masses very distinctly. The diagnosis of recurrent hypertrophied adenoids should not be made

TABLE 38. FOCAL INFECTION ALONE AND IN COMBINATION IN 400 ASTHMATIC CHILDREN

Cause of asthma	Per cent
Infection (alone and combined)	
Infection	30.50
Infection plus inhalant	44.25
Infection plus food	4.75
Infection plus inhalant plus food	7.75
Total	87.25
Inhalant (alone and combined)	
Inhalant	10.25
Inhalant plus infection	44.25
Inhalant plus food	2.25
Inhalant plus infection plus food	7.75
Total	64.50
Food (alone and combined)	
Food	0.25
Food plus infection	4.75
Food plus inhalant	2.25
Food plus inhalant plus infection	7.75
Total	15.00

SOURCE: Chobot and Uvitsky.

by palpation which is both painful and inaccurate. Large masses of adenoid tissue can be treated only by surgical removal. Local applications of radium can be effective only when the tissue is small in quantity and well localized. X-ray therapy is most satisfactory for the disseminated spread of lymphoid tissue over the nasopharynx.

Occasionally one hears it said that a tonsillectomy precipitated asthma but in my opinion the operation was performed in such an instance because the child was already suffering from some respiratory complaint. The onset of asthma then was part of a natural sequence of events and probably would have occurred anyway.

Cooke and Grove[1] showed that chronic infection stimulates the growth of the lymphoid tissue (For further discussion of tonsillectomy in the allergic child see Chap 54)

Prompt treatment of purulent sinusitis is indicated to prevent the chronic hyperplasia that so frequently appears in the adult as a result of inadequate allergic and sinus therapy It is important to realize that preventive measures in childhood will often forestall both asthma and surgery later In cases with purulent sinusitis antral irrigation should be done and autogenous vaccine prepared from bacteriologic cultures

It is frequently asked at what age treatment should be undertaken My answer is that it should be undertaken at the earliest possible moment and that tonsillectomies when indicated may be performed after the age of eighteen months It is true that infective asthma in infancy may occasionally be self limited but this outcome should never be depended on

Treatment other than surgical removal depends on vaccine therapy Properly prepared autogenous vaccines should be administered after infected foci have been removed The use of vaccine therapy has been the subject of considerable discussion in pediatrics but a vaccine properly made from tissue cultures or from sputum or laryngeal swabs is of greater value than stock vaccine In infants under eighteen months old vaccine therapy is instituted first since the child is too young for surgery

The vaccines are best prepared from cultures that are killed by heat Usually there are several organisms in the culture These are combined in equal parts and diluted with saline to a 1 per cent suspension

The most important and most troublesome aspect of treatment is the prevention of colds When some member of the family or a nurse or maid has a chronically infected sinus the child is readily reinfected Most physicians today examine nursemaids for tuberculosis but it is equally important to check for sinusitis when it is an asthmatic child that is being cared for

A valuable measure for controlling recurrences of infection is the daily use of sulfadiazine Sensitivity to sulfadiazine is rare but it may appear as fever hives dermatitis renal irritation or leukopenia Some supervision must be exercised with a child taking sulfadiazine Blood counts and urinalysis should be done every two weeks Other antibiotics may be used with proper precaution

Epinephrine 1 1 000 by subcutaneous injection in doses of 0 1 to 0 3 ml repeated if necessary is the most effective method of controlling an attack of asthma In children small doses repeated at

quent intervals are far better than a large dose which may upset child and induce tremor pallor and vomiting

Ephedrine is of great value in the mild attack In young children s best administered as a 3 per cent aqueous solution Dosage is ally 15 to 20 minims three times a day Its advantage over epi hrine lies in the fact that it can be administered orally

odides are an old and good remedy Dosage is 3 to 10 grains in er orally three times daily They frequently give excellent re ts and are of greatest value when bronchial secretion is scant ey act by liquefying the bronchial secretion and so loosen the igh

Aminophylline in the form of a rectal suppository is of great help young children when it is desirable to avoid injecting epineph e A dose of 1½ to 3 grains is adequate It may be combined h ¼ or 1/ grain of codeine and repeated at four or five hour ervals

Aspirin should never be used in cases of asthma without *finding* whether it has been tolerated previously Violent reaction may ow its ingestion and deaths have been reported[3] The first dose uld never exceed 1/10 grain

The adrenocortical hormones are of great value in controlling a ere attack but must never be used for long periods of time in ldren (see Chap 34 and 57)

t is important that the wholehearted cooperation of the parents sought Parents must be made aware of the causes of the child s ma the results of his tests and the need for persistent treat nt possibly extending over a long period of time It may be nec ry to stress the fact that intercurrent respiratory infection can se asthma irrespective of any other cause Early removal of in ed foci must be stressed as the only basis for therapy of infectious ma

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Bret Ratner *

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INFANTILE ECZEMA

There is a greater susceptibility to allergy in children born of highly allergic families The actual relation of this to genetic factors remains to be evaluated however In allergic infants under one year of age the author found that eczema was the presenting syndrome in 90 per cent of the cases[1] The average age of onset of eczema in infants under a year was 1 9 months and the average age at the time of observation was 6 5 months It is of further interest to note that of all the allergic syndromes the period between the age of onset and the time that medical attention is sought is shortest for eczema In this study of 250 allergic children 45 per cent suffered from eczema whereas in the adult allergic antecedents of these patients the number of cases with eczema was only about 10 per cent showing that this disease is particularly related to childhood From these figures it is apparent that eczema is the prevailing allergic condition in infancy and that it starts considerably earlier than any other allergic syndrome[1]

Before making a diagnosis of allergic eczema in infants one must rule out many other dermal conditions such as seborrheic dermatitis impetigo contagiosa sudamina and skin irritations due to mechanical factors or excessive use of skin oils

A dermatitis due to allergic sensitization is variously known as eczema infantile eczema atopic eczema atopic dermatitis allergic dermatitis or disseminated neurodermatitis This should be distinguished from the irritative dermatitis or contact dermatitis due to a primary irritant which in a given concentration or under given

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* Deceased

circumstances will affect practically all human skins Thus a nonallergic contact dermatitis can be caused in the normal skin by contact with a physical or chemical agent Examples are the typical diaper rash seen in early infancy and the dermatitis resulting from mechanical pressure or irritation Such a dermatitis is characterized by inflammation of varying degrees of intensity which may cause the destruction of the percutaneous layers and even the subjacent tissue The localization and relation to the causative factors makes these conditions readily recognizable and elimination of the offending factors affords relief

Typically infantile eczema presents an erythematous and oozing appearance which involves the face and scattered areas on the body and extremities It may be localized or it may affect practically the entire body The condition is highly pruritic and this is perhaps the outstanding feature Evidence of bleeding and scratch marks and crusts of congealed blood and serum are the rule

Most infantile eczemas clear up by the end of the first year However if the dermal manifestations persist beyond the second year they may be succeeded by allergic respiratory symptoms This syndrome which the author has designated the *dermal respiratory syndrome* is significant A number of years ago it was thought that the eczema of early childhood was due largely if not entirely to sensitization to foods Since more comprehensive testing has been done in children with allergic disorders it has been learned that even young infants with eczema are sensitive not only to foods but also to inhalants and contactants The allergic dermal respiratory syndrome may be defined as a symptom complex in which both dermal manifestations (urticaria or eczema) and respiratory (perennial rhinitis hay fever asthma) may occur in the same patient either concurrently or at different periods

Of all allergic children studied by the author 35 per cent presented this symptom complex and of those cases of allergic eczema in which there were positive reactions to inhalant substances 59 per cent subsequently developed respiratory allergy[2] It is evident therefore that eczema in childhood should not be regarded solely as a dermatologic condition for a substantial proportion of these patients develop either asthma or hay fever

The dermal respiratory syndrome may be divided into several categories

1 Those cases mostly in infants which present dermal manifestations alone with negative skin reactions to inhalants

2 Those cases which present dermal manifestations with positive skin reactions to inhalants but in which respiratory allergy has not yet developed

3 Those which present both dermal and respiratory allergy with negative reactions to inhalants

4 Those with both dermal and respiratory manifestations and positive reactions to inhalants

The last group usually is composed of older children whereas the first three groups are largely made up of infants This distribution of cases suggests the manner of evolution of the dermal respiratory syndrome

An interesting parallel study was reported by Vowles Warin and Apley of London [4] They studied 84 cases with follow up visits to the home from thirteen to twenty two years after the patient s ad *mission to the hospital with infantile eczema* Asthma *recurrent* bronchitis and seasonal hay fever were present in 73 per cent of their patients as compared with 5 to 7 per cent of a control group

The chronic form of eczema which is best designated as allergic disseminated neurodermatitis is perhaps the most difficult form to eradicate It tends to become localized in the neck the flexures of the arms and legs and the dorsa of the hands The lesions assume chronic characteristics in the form of papules fissures excoriations lichenifications and dark grayish plaques They are very pruritic and the skin shows evidence of injury from scratching

Positive allergic reactions are the rule The offending allergens are multiple most important among them being the inhalants and contactants It should be borne in mind that pollens can definitely be a causative factor in seasonal eczema

In all chronic eczemas psychogenic factors play an important role

Perhaps the most difficult problem to combat in chronic eczema is the inevitable presence of secondary dermal infections usually due to staphylococci and fungi Even in the presence of a truly al lergic dermatitis there may be superimposed other dermal condi tions such as seborrhea Kaposi s varicelliform eruption impetigo contagiosa moniliasis trichophytosis epidermophytosis pyogenic infections scabies pityriasis rosea *molluscum contagiosum* derma titis venenata dermatitis resulting from overmedication and su damina

These secondary and concomitant conditions must be treated spe cifically *The importance of careful differential diagnosis is stressed* for specific treatment may eradicate a condition which has been mistakenly diagnosed as an allergic eczema This is particularly im portant when dealing with widespread sudamina scabies trichophy tosis and secondarily infected dermatitides of various origins

The immediate treatment of infantile eczema can be undertaken without elaborate allergy testing However if the eczema does not yield to these simple medications the child should be studied in

tensively to determine the specific offending allergens responsible for the continuation of symptoms These diagnostic studies and the institution of antiallergic therapy are important not only to eradicate the eczema but also to prevent the development of respiratory allergy

Progress has been made in the specific diagnosis and treatment of eczema since the advent of the allergic skin test In the authors studies 85 per cent of infants under one year of age gave positive dermal reactions Of these 41 per cent reacted to foods alone and 59 per cent to a combination of foods inhalants and contactants

The passive transfer test that is testing for antibodies in the child s serum by transferring it to the recipient s skin has been found of only limited value Humoral antibodies to the offending substances are not always found in the blood of sensitive infants The direct test in my experience gives much more positive results

While the child is being treated with wet dressings lotions or ointments the body should be completely covered At times complete restraint may be essential the hands and legs being secured to the crib slats I have found that bathing with a bland soap and water is not contraindicated

If secondary infection is present antibiotics can be used orally

Because of the absorption and toxicity of boric acid and crude tar it is best not to use these medicaments for young infants with wet oozing eczema

Under no circumstance should an eczematous infant or child be vaccinated against smallpox nor should such patients be permitted to come in contact with a freshly vaccinated person Eczema vaccinatum may develop and this condition may be serious at times even resulting fatally

There are a number of infants who have a dry skin with a sandpaper like appearance They appear to be suffering from eczema Such infants may actually have a thyroid deficiency A study of the hand bones by x ray may disclose retardation in bone maturation In such instances the judicious use of thyroid is indicated and may result in a correction of the basic skin disturbance

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ADENOTONSILLECTOMY IN THE ALLERGIC CHILD

The problem of adenotonsillectomy in the allergic patient is a much disputed one The often asked question What will the removal of the tonsils and adenoids do to my child's allergies? is answered in any of three ways depending on the particular point of view of the allergist Operation will improve the allergic condition operation will aggravate the allergic condition or operation will not make any difference to the basic allergic picture These schools of thought can be summarized as follows

1 One group believes that the tonsils and adenoids can and often do act as foci of infection[1] - If these lymphoid tissues are infected in an allergic patient they should be removed as early as possible It is believed that prompt removal can favorably influence asthma and furthermore can prevent asthma in a potentially asthmatic individual Attention is paid to allergenic testing desensitization and environmental control in evaluating the allergic picture However stress is placed on the early removal of the tonsils and adenoids in all patients when infection of the lymphoid tissues complicates the allergy

2 A second school believes that the tonsils and adenoids play an important role in preventing the spread of infection from the upper respiratory passages to the lower respiratory tract[3, 4] They believe that the tonsils and adenoids play an important role in the first line of defense in infections of the nose and throat It is believed that removal of tonsils and adenoids may precipitate asthma in an al

lergic individual Furthermore removal of the tonsils and adenoids may convert a mildly asthmatic patient into a severely asthmatic patient They contend that tonsillectomy is fraught with danger because of the possibility of intensifying the allergic process While the tonsils and adenoids are frequently infected they believe that these lymphoid tissues drain the infection from the nose and throat thereby delaying or preventing the spread to the bronchial tree The adherents of this school advise a thorough allergic investigation anti infective therapy and avoidance of removal of tonsils and adenoids in the allergic patient

3 The third group believes that indications for adenotonsillectomy are the same for allergic as for nonallergic patients[5-8] When the tonsils and adenoids are chronically diseased or abnormally enlarged they should be removed regardless of the underlying allergic state When tonsillectomy is performed primarily with the hope of altering the allergic process the results are doomed to failure They believe that the tonsils and adenoids have no bearing on the fundamental allergic process A patient with allergies and infection should be treated with allergenic measures and antibiotics If indications for tonsillectomy still persist after a course of allergic management surgery should be performed

It should be noted that there are those who do not believe in immediate surgery for either the allergic or the nonallergic patient They believe that adenotonsillectomy can as a rule be avoided if infection is completely eradicated[9, 10] by (1) specific antibiotics given orally or parenterally or by aerosols (2) control of family contact infection and (3) elimination of infections in other sites of the body In the allergic patient antiallergic measures would also be applied Surgery is resorted to only if these measures have failed

As can be seen from the above a difference of opinion exists on the indications for adenotonsillectomy in the allergic patient More workers appear to be adherents of the third group On comparing asthmatic patients with intact tonsils and adenoids and adenotonsillectomized patients no statistical difference is found in the severity of asthma Both groups show the same percentage of mild moderate and severe cases of asthma If the tonsils and adenoids play such a protective role in preventing the spread of infection from the nose to the lungs there should be less severe asthma in the group with intact tonsils and adenoids Conversely if the tonsils and adenoids play such an important role as foci of infection there should be a lower incidence of severe asthma in the adenotonsillectomized group These studies indicate that the presence or absence of the tonsils and adenoids has no bearing on the basic allergic problem

the generally accepted indications for adenotonsillectomy in the al lergic patient are therefore the same for allergic as for nonallergic patients The adherents of this school give the following indications for surgery in both the allergic and the nonallergic patient

1 Chronic infection of the tonsils and adenoids

2 Marked enlargement of tonsils and adenoids interfering with breathing and swallowing

3 Persistent enlargement of the cervical glands due to upper respiratory infection

4 Recurrent ear infections

5 Hearing loss due to enlargement of the adenoids and other nasopharyngeal lymphoid tissue

6 Repeated upper respiratory infections associated with cardiac and renal pathology

There is a special contraindication however to adenotonsillec tomy in the allergic patient Operations should never be performed during periods of pollination i e April through October in the northeastern part of the United States The result of such ill timing may be initiation of asthma in a patient with allergic rhinitis or existing asthma may be aggravated

When a patient is first treated for allergy and infection it is ad visable to delay decision regarding immediate removal of the tonsils and adenoids Other measures should be tried first The infection must be vigorously combated This may involve culture and sensi tivity studies in order to determine the specific antibiotics required for the offending organisms When the allergic patient is treated by removal of environmental allergens specific food elimination and desensitization along with specific antibiotics the need for ade notonsillectomy often disappears

It is of interest that about 40 per cent of patients who come to an allergist s office for treatment have already had an adenotonsillec tomy Often this was performed for the relief of allergic symptoms without success In contrast some allergists find that only 4 to 8 per cent of patients require removal of the tonsils and adenoids after adequate antiallergic and anti infective measures have been insti tuted Other allergists report that there is no need to send any pa tients for adenotonsillectomy after antiallergic and anti infective treatment

It is important to remember that allergic patients are highly sus ceptible to infection They have nasal mucous membranes that are swollen and boggy and because of the swelling of the nasal mucous membranes secondary infection may occur Stasis and obstructions of the nasal passages from allergic and nonallergic causes lead to in

fection What may masquerade as primary chronic infection may be allergy with secondary infection Unless the allergic picture is recognized and treated the infection will return or persist to plague the patient as well as the physician Adenotonsillectomy will not control the tendency to secondary infection if the basic allergy is not controlled It is important to attack all infection vigorously in allergic people but the primary approach should not be removal of the tonsils and adenoids

When a patient has regrowth of nasopharyngeal lymphoid tissue it is wise to suspect an underlying allergy About 7 per cent of patients who come to an allergist s office have had more than one adenotonsillectomy Repeated surgery was performed to remove the lymphoid hyperplasia without recognizing the underlying allergic basis It is important to know that allergic patients with or without secondary infection frequently have a tendency to lymphoid hyperplasia of the nasopharynx Surgical removal or irradiation does not alter this recurrence of hyperplasia

Chronic postnasal drip persistent rhinorrhea nasal obstruction and frequent colds may be signs of chronic infection or allergy Unfortunately these are too readily accepted as indications for adenotonsillectomy Too often the allergic cause is not recognized Surgery will not result in improvement of these symptoms if the basic cause is allergy

The differential diagnosis between infection in the nose and allergy is often difficult Detailed history family background and physical examination are important An additional very helpful tool in arriving at a correct diagnosis is microscopic examination of the nasal smear for eosinophils A total of more than 4 per cent eosinophils is suggestive of allergy In pure infection the nasal smear shows predominantly polymorphonuclear cells in allergy the smear consists mainly of eosinophils in infection superimposed on allergy the smear is predominantly polymorphonuclear with or without the eosinophils However with the subsidence of infection the allergy comes to the foreground with return of the eosinophils It should be routine to do repeated nasal smears in all cases where allergy may be a primary or secondary factor When the nasal smear is positive for eosinophils antiallergic treatment should be instituted along with adequate antibiotic therapy for the concomitant infection (see also Chaps 17 18 27)

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55 | *Solomon Slepian*

ALLERGY AND GERIATRICS

The literature on allergy in the aged is sparse because the manifestations of allergy are much the same as are found in younger age groups; nevertheless, there are some aspects of the subject worth discussing.

It is generally recognized that some diseases are prone to occur at certain periods of life. Thus allergic diseases seem to be predominantly a disturbance of the young and middle aged. This, however, does not mean that allergy may not manifest itself for the first time in an old person or that the various allergies may not continue to be active in the later years of life. The incidence of certain of the allergic manifestations differs, however, in the aged as compared to young people. Moreover, there are certain features in the character of allergic conditions in the aged which require special awareness by the physician who treats geriatric patients. Among these features are:

1. The seeming benignity of allergy in general in old people.
2. The difficulties in the interpretation of skin tests in the aged.
3. The greater hazard to life of asthma starting late in life as compared to asthma in the young.
4. Precautionary measures to be taken in the medical management of allergy in the aged.

ATTENUATION OF SYMPTOMS

It seems to be generally true that in persons who have had allergies from early life symptoms lessen with advancing age or at times

disappear entirely This may occur without specific treatment or general allergic management The loss of symptoms with age may come about because specific sensitivities have a tendency to be of limited duration and wear out so to speak It may at times take many years for this to happen But while sensitivity to some substances disappears hypersensitiveness to others may become manifest There is also the possibility of sensitivities taking a new form that is producing a new type of clinical response A patient may cease having nasal allergy from a specific food but find that he now gets urticaria or gastrointestinal symptoms from the same substance

Why this apparent attenuation of the allergic state occurs is not clear It might be (but we have no proof) that as a consequence of the aging process in some individuals the cells in the shock tissue because of endogenous changes lose the ability or do not have the vitality to support a vigorous immunochemical reaction Yet the immunology of the allergic state that is the fundamental physicochemical reactions which result in the clinical manifestations of allergy is said to be the same in the geriatric patient as it is in the young only the threshold may be altered

Not all allergists agree that there is a spontaneous lessening of the allergic state in the aged Urbach[1] feels that in retirement aged persons are removed from exposure to the hazards of industrial allergens Retirement may have also a salutary psychological effect on many old people It is for these reasons he believes that there is an apparent lessening of their allergies

SKIN TESTS

When skin tests are employed to detect offending allergens the geriatric patient presents a special problem Even in the young patient some allergists rely very little on a positive skin test to determine the allergen in a given case except in testing for pollen sensitivity In the aged the reliability of the skin test is even more questionable The dry atrophic skin of the senescent person reacts poorly to allergens The scratch test particularly gives feeble reactions and the incidence of positive reactions to foods becomes less in older people although in many instances the clinical symptoms and the therapeutic results from food elimination seem to indicate hypersensitiveness to food as the causative agent

Nevertheless we must be aware of the occasional aged patient who responds very actively and severely to skin tests Wiseman and McCarthy Brough[7] report the death of a seventy eight year-old woman following intradermal testing They emphasize that the aged

person requires the same meticulous care in testing and treatment as the patient in any other age group In spite of the fallibility of skin tests they should be made in any case where the offending substances cannot be detected by other methods

LATENT ALLERGY

In the majority of instances where it is claimed that allergy has started late in life minor allergic symptoms have been present but unrecognized in early life Only the involvement of a new shock tissue with the development of new symptoms has in these cases made the patient suddenly aware of a previously existing but unrecognized allergic condition For example asthma may develop late in life in a patient who has had mild nasal symptoms for many years Unless a very careful history is taken it will not be apparent that the asthma in this instance is simply the involvement of a new shock tissue in a hypersensitive individual and not the initial manifestation of allergy

SEVERITY OF ASTHMA

Asthma either atopic (immediate wheal reaction and strong familial tendency) or nonatopic is the most important of the allergic diseases in old people Its prognosis appears to become more serious with the age at onset In young and early adult life asthma is rather easily controllable and is benign as far as danger to life is concerned in spite of its alarming morbidity Bullen[3] studied 176 deaths in which asthma was a primary or contributing cause or in which there was a definite history of asthma in the past He found that in these persons the onset of asthma was in the fourth fifth or sixth decade in contrast to the usual age of onset of atopic asthma which is in the first decade In more than half the patients studied death occurred within ten years of the onset of symptoms The majority of the cases were of the nonatopic type in contrast to the atopic form of asthma which starts in childhood It is obvious from the rapid decrease in the length of life of patients whose asthma started after the age of forty that asthma in later life presents a much more serious hazard than that which begins in youth

This seems to be directly related to the fact that in patients with uncontrolled asthma the hazard is greater for frequent attacks produce scarring and extensive fibrosis and emphysema of the lungs The progressive involvement of the vascular tree resulting from these morbid changes leads to hypertension of the lesser circulation and frequently sclerosis of the pulmonary vessels This may even

tuate in right sided cardiac failure The greater susceptibility of the older age group to repeated serious respiratory infections is also an added hazard reflected in the mortality figures

It should be mentioned also that in older patients a number of clinical conditions occur which produce respiratory distress and wheezing and which may be misdiagnosed as allergic asthma These are chronic bronchitis and emphysema bronchiectasis cardiac asthma due to left ventricular failure pulmonary sclerosis tracheal and bronchial obstruction or impingement due to mediastinal tumors diverticulum of the esophagus and bronchogenic tumor Any of these conditions may of course be found in young people but they are more often encountered in the geriatric group In addition to simulating asthma one of these conditions may complicate an already existing allergic asthma of the atopic (hereditary extrinsic) or nonatopic (acquired intrinsic) variety In such an event the diagnosis and management becomes much more difficult

Persons with heart disease and allergic asthma who have attacks of paroxysmal nocturnal dyspnea present a problem in diagnosis This is often encountered in geriatric patients since the incidence of cardiovascular disease is high in old people It is imperative to evaluate this situation accurately since the treatment of cardiac failure is different from and its prognosis more serious than that of allergic asthma The life expectancy of patients once they begin to have attacks of cardiac asthma is about one and one half years The allergic attack is by comparison benign and a good prognosis can usually be given to an anxious family If the asthmatic attacks in an individual are mild for many years and then become more severe at night with little or no change during the day cardiac asthma should be suspected In cardiac asthma the paroxysmal dyspnea is due to left heart failure The attack occurs suddenly with an extreme sense of suffocation and fear of death There is a previous history of heart disease angina pectoris hypertension or renal disease The heart is usually enlarged The rales are of the moist rhonchi or bubbling variety mostly limited to the bases and there is cough with a frothy or pink sputum (Further discussion of cardiac asthma is given in Chap 25)

HAY FEVER

It is commonly believed that seasonal hay fever does not develop in old people This is generally true in the majority of old persons who have seasonal hay fever it is carried over from early life But nearly all allergists have on occasion treated patients whose hay fever started late in life In a study of 222 adult seasonal hay fever

sufferers it was found that about 1 8 per cent began to have symptoms for the first time after the age of fifty[4] Hansel[5] found in a group of 220 patients of age 15 and over with nasal manifestations of allergy that in 8 6 per cent the symptoms began between ages fifty one and sixty five The management of seasonal hay fever in the aged does not differ from that in the younger group

Nasal allergy ranks next to asthma in importance as an allergic manifestation in elderly people but its incidence is much lower than in young persons In senescence there occurs a thinning of the nasal mucous membrane and a destruction of the ciliary action the epithelial layer becomes thin and devoid of blood vessels and the submucuous glands become small and atrophic Since the basic allergic reaction involves the vascular bed and glandular structures the senescent nasal membrane apparently may lose the capacity to act as a shock organ The morphologic changes may create a situation unfavorable for the manifestation of allergy

The pale appearance of the turbinates and other nasal mucosa and the accompanying nasal discomfort in old age should not be mistaken for allergy The pallor is associated with dryness and the presence of incrustations whereas the allergic membrane has a bluish gray pallor and appears boggy

Taub[6] feels that there are older women with perennial nasal allergy in whom an endocrine factor is responsible for the nasal symptoms He also speaks of a well-defined group whose symptoms occurring during the aging period of life are due to physical allergy They have a hypersensitivity to cold heat or light

MISCELLANEOUS FORMS OF ALLERGY

Allergy of the skin is not prominent in geriatric patients although urticaria angeoneurotic edema and contact dermatitis do occur The most outstanding of the allergic dermatoses namely atopic eczema rarely begins after the age of thirty

In institutions for the aged the allergist sometimes sees patients with generalized pruritus with no visible skin lesions—patients in whom organic diseases usually associated with pruritus have been excluded In most instances a personal history of allergy cannot be elicited nor can any clues be obtained from the interview as to diet contacts or medications as a possible cause for the itching These patients have been considered to have senile pruritus on a nonallergic basis However Percival[7] places senile pruritus in the category of allergy He finds this more common in the lean or emaciated patient than in the well nourished

An individual may be intermittently exposed to a contactant for many years without a reaction then develop a dermatitis even as late as the seventh or eighth decade upon massive exposure to the substance Contact dermatitis produced in some older women by hair dye and cosmetics may fall into this category as well as poison ivy dermatitis Contact dermatitis when it occurs in old people appears to run a more protracted course than in younger people

Gastrointestinal allergy has no special features referable to old age It is not a major problem in old persons but allergy must be kept in mind as a possibility when a geriatric patient presents bizarre abdominal symptoms not traceable to an organic pathologic condition

Deafness common in old people may rarely be due to Ménière s disease based on allergy Vascular headaches due to hypersensitiveness common in young adults also occur in the aged though less frequently

PRECAUTIONS IN TREATMENT

Elderly male patients with prostatic hypertrophy are intolerant to ephedrine because of its effect on bladder tone and consequent dysuria In such patients this drug must not be pushed for acute urinary retention may be precipitated with severe consequences Other bronchodilators such as aminophyllin or Isuprel should [illegible] substituted

Steroids while very useful in allergy must be employed with [illegible] care particularly in the geriatric patient whose adrenals are al[illegible] partially atrophied There is only a small margin of safety [illegible] signs of adrenocortical exhaustion or frank failure appe[illegible] fractures due to cough are not uncommon in old peop[illegible] steroids The calcium and protein depletion produced [illegible] drugs in bones already the seat of osteoporosis consequ[illegible] may result in extremely fragile bones The incidence of [illegible] berculosis is much higher in the later years of life and [illegible] tion of this disease may produce dire results

Epinephrine in the presence of hypertension is [illegible] versial drug There should be no hesitancy about [illegible] rine in doses of 0 2 to 0 3 ml repeated if necessa[illegible] an [illegible] hypertensive patient to cut short an asthmatic att[illegible] The [illegible] precipitating a vascular accident severe angina [illegible] bosis from such small doses is not great and is [illegible] the strain and exhaustion of a prolonged asthm[illegible]

The danger of morphine in asthma is well [illegible] is even more dangerous in the geriatric patien[illegible]

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PART FIVE

GENERAL TREATMENT AND PROPHYLAXIS IN ALLERGY

Selian Hebald *

56

SPECIFIC INJECTION TREATMENT OF HAY FEVER AND ASTHMA

Patients with seasonal hay fever show positive skin reactions to extracts of the offending pollens In asthma skin testing will reveal one or more allergens to which the patient is sensitive in about half the cases The incidence of positive skin reactions is greater among asthmatics of the younger age group In the age group over forty positive skin reactions are much less common since at this age asthma is more often due to respiratory infection rather than to ex ternal allergens However in many patients asthma is due to a com bination of infection and external allergen sensitivity and in such cases both causes must be treated When an external allergen can be detected avoidance is the ideal treatment Often this is impossible or impractical and it is in these cases that specific injection treat ment is the best available method of protection for the allergic patient

The allergens most commonly used in specific injection treatment are the pollens house dust (either a stock mixture or dust from the patient s home) chicken duck or goose feathers the danders of dog cat rabbit and horse and the spores of molds Dust is probably the most common specific agent causing allergic rhinitis and asthma The irritant in it seems to be different from all the known sub stances and has not yet been identified The common mold spores causing symptoms in this area are *Alternaria* and *Hormodendrum*

* Deceased

Silk and goat epithelia are rarely used for hyposensitization Orris root which was frequently used for specific injection treatment years ago is no longer a common offender today since cosmetic manufacturers rarely use it now in the manufacture of their products All these substances may cause asthma or rhinitis or both in sensitive patients There are other allergens such as cottonseed and kapokseed to which acute sensitivities are sometimes encountered These two materials are found in upholstered furniture mattresses and stuffed toys Complete removal of these articles from the home is the procedure of choice Specific treatment with extracts of these seeds is dangerous and should not be attempted

Specific injection therapy is not necessary for foods except those of the cereal group (wheat rye corn and rice) which cause asthma and rhinitis by inhalation in bakers and cooks Patients who react to cereals by inhalation can usually eat them without trouble

In the northeastern area of the United States there are three pollen seasons for hay fever—spring early and late (see Chap 16)

Often patients who clinically have one type of seasonal hay fever such as ragweed in addition show positive skin reactions to the grasses and/or the trees without ever having had clinical hay fever during the grass or tree season Such positive skin reactions should be regarded only as potential causes of trouble These patients frequently develop clinical hay fever to the additional pollens at a future date and should be advised concerning this possibility However they should not be treated with pollens which are not causing clinical symptoms Patients who are sensitive to the pollen of only one season both clinically and on skin test not infrequently develop positive skin reactions and clinical sensitivity to the pollen of other seasons in subsequent years

The general principle of injection treatment is to give gradually increasing doses which must be adjusted to the patient s tolerance The *intracutaneous skin test* is a guide both to the patient s sensitivity and his tolerance to dosage This test is graded as *marked* (skin redness itching and showing pseudopods) *moderate* (skin redness and itching but no pseudopods) *slight* and *negative* A marked reaction signifies confirmation of sensitivity when associated with a positive clinical history Moderate and slight reactions call for investigation with stronger extracts Completely negative skin tests to the extracts of pollens danders dusts and molds signify that these allergens are not the cause of the patient s symptoms

Patients may be divided into three classes according to their skin sensitivity as determined by the strength of extract which is required to produce a marked reaction Patients showing a marked

reaction with an extract containing 10 protein nitrogen units per milliliter are classified as Class A or hypersensitive Those showing a marked reaction to 100 units are Class B or sensitive while those requiring 1 000 units to produce a marked reaction are Class C or moderately sensitive If a marked reaction is elicited with a certain concentration testing beyond this point is contraindicated Patients are first tested intracutaneously with a 10 unit extract and observed for twenty minutes before being tested with a 100 unit extract or a 1 000 unit extract if so indicated Skin testing is performed by the intracutaneous technic a small wheal (0 01 ml) being raised on the outer aspect of the arm *Scratch tests* with powdered extracts may also be used to ascertain sensitivity These are usually done on the inner aspect of the forearm

TABLE 39 AVERAGE DOSAGE ACCORDING TO DEGREE OF SENSITIVITY

	Dosage (protein nitrogen units per ml)		
Dose number	Class A marked reaction to 10 units	Class B marked reaction to 100 units	Class C marked reaction to 1 000 units
1	2	10	25
2	5	20	50
3	10	40	100
4	15	80	[illegible]00
5	20	1 5	400
6	30	00	600
7	50	300	800
8	70	500	1 000
9	100	700	1 500
10	150	1 000	2 000
11	250	1,500	3 000
12	400	2 000	4 000
13	600	3 000	6 000
14	800	4 000	8 000
15	1 000	5 000	10 000

1 unit equals 0 00001 mg protein nitrogen per ml

Table 39 gives the average dosage for patients according to degree of sensitivity as determined by skin tests Dosage is given in protein nitrogen units per milliliter 1 unit equals 0 00001 mg protein nitrogen per milliliter This schedule may be used for the administration of all pollens molds and animal danders

Extracts standardized by other methods such as total nitrogen weight by volume and Noon units may be administered in the

same general manner. Dust extracts, however, are not usually standardized but put up in a concentrate, 1:10 and 1:100 dilutions. Treatment is usually begun with a 1:100 dilution and is gradually increased to a maximum of 0.5 ml. or more of the concentrate.

It should be remembered that many patients are highly sensitive and their maximum tolerated dose will be smaller than that in the table. While it is true that those who take their dosage well and reach a large maximum dose generally have a better clinical result, it is also true that highly sensitive patients on a small maximum dosage may also have good clinical results.

Injections are given at four- to seven-day intervals subcutaneously in the outer aspect of the arm, middle and lower thirds. Syringes graded in tenths of a milliliter should be used in treatment. A ¼ inch 26 gauge or slightly larger needle may be used.

In seasonal hay fever it usually takes about 15 *injections* to reach maximum dosage. Treatment should commence approximately three months before the pollinating season, so that this dosage is reached when pollination commences. Injections should be continued through the season. It is not necessary to reduce dosage during the season except in some patients who are highly sensitive.*

Patients may stop therapy at the end of the season and begin again in the spring of the following year, or they may be treated perennially. Under *perennial therapy*, when the maximum dosage is attained, this dose is administered at three- to four-week intervals throughout the year, with the interval reduced to two weeks during the season. If the interval runs beyond four weeks, dosage must be correspondingly reduced and then carefully increased during subsequent visits at about two-week intervals. Satisfactory results with perennial treatment are about 10 per cent higher than those obtained with preseasonal treatment. When changing to a freshly made extract, dosage should be reduced to one third or one half the previous amount given and then gradually increased to full dosage. Perennial treatment is not recommended in patients who are very sensitive and whose maximum dosage is small. Patients may also be treated coseasonally, although they start late, even after their pollinating season begins. Small doses carefully increased at two- or three-day intervals to the end of the season often produce worthwhile clinical benefit.

One should proceed very slowly at first in patients who have never received treatment with the specific allergen being administered.

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* Editor's Note: Not all allergists accept this opinion. Many reduce the dosage by one third or one half for some patients.

Marked local reactions often occur at the beginning of treatment and it sometimes takes numerous injections with very little increase in dosage before the normal schedule can be followed Patients should always be asked the extent and duration of the local reaction at the site of the previous injection Increase in dosage is judged accordingly and treatment is highly individualized Children usually tolerate high dosages well In treating a pregnant patient the dosage should be reduced to one third or one half the usual schedule and dis continued when the season is over Perennial treatment is not rec ommended during this period

About one third of hay fever patients suffer from asthma when they are untreated Injection therapy usually controls this very well A satisfactory clinical result can be obtained in about 85 per cent of treated hay fever patients Winter colds and sinus infections are often greatly reduced when hay fever is properly treated

Some patients lose their clinical hay fever after several years of treatment but many more continue to require treatment most of their lives It is good policy to retest the hay fever patient once a year A patient under treatment who goes through two or three seasons without any symptoms and whose reactions to skin tests are greatly de creased almost to negative may be regarded as clinically cured There are many such patients However some of these cured pa tients after being entirely well for several years return with full blown clinical symptoms and again show marked skin tests to the pollen to which they were previously sensitive

Bacterial vaccines autogenous and stock are important agents of therapy especially in infective asthma The autogenous vaccines are usually made from infected tissues of the nasal accessory sinuses after operation antral washings and sputum cultures The labora tories usually make them in strengths of two to five billion killed organisms per milliliter or a 1 per cent suspension These vaccines should be diluted down to 1 1 000 for beginning treatment They may be very potent and should be given in carefully graded doses up to about 1 ml of a 1 10 dilution This maximum amount may then be given at three to four week intervals on a perennial basis Skin testing with bacterial vaccines gives us no reliable information and so cannot serve as a guide to therapy

Systemic or *constitutional reactions* resulting from injections occur occasionally in the course of treating the allergic patient Most re actions occur within thirty minutes after an injection The first signs of a constitutional reaction usually are itching of the palms of the hands itching of other parts of the body sneezing coughing and facial redness Other symptoms may be urticaria angioedema and

same general manner Dust extracts however are not usually standardized but put up in a concentrate 1 10 and 1 100 dilutions Treatment is usually begun with a 1 100 dilution and is gradually increased to a maximum of 0 5 ml or more of the concentrate

It should be remembered that many patients are highly sensitive and their maximum tolerated dose will be smaller than that in the table While it is true that those who take their dosage well and reach a large maximum dose generally have a better clinical result it is also true that highly sensitive patients on a small maximum dosage may also have good clinical results

Injections are given at four to seven day intervals subcutaneously in the outer aspect of the arm middle and lower thirds Syringes graded in tenths of a milliliter should be used in treatment A ¼ inch 26 gauge, or slightly larger needle may be used

In seasonal hay fever it usually takes about 15 injections to reach maximum dosage Treatment should commence approximately three months before the pollinating season so that this dosage is reached when pollination commences Injections should be continued through the season It is not necessary to reduce dosage during the season except in some patients who are highly sensitive *

Patients may stop therapy at the end of the season and begin again in the spring of the following year or they may be treated perennially Under *perennial therapy* when the maximum dosage is attained this dose is administered at three to four week intervals throughout the year with the interval reduced to two weeks during the season If the interval runs beyond four weeks dosage must be correspondingly reduced and then carefully increased during subsequent visits at about two week intervals Satisfactory results with perennial treatment are about 10 per cent higher than those obtained with preseasonal treatment When changing to a freshly made extract dosage should be reduced to one third or one half the previous amount given and then gradually increased to full dosage Perennial treatment is not recommended in patients who are very sensitive and whose maximum dosage is small Patients may also be treated coseasonally although they start late even after their pollinating season begins Small doses carefully increased at two or three day intervals to the end of the season often produce worthwhile clinical benefit

One should proceed very slowly at first in patients who have never received treatment with the specific allergen being administered

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EDITOR'S NOTE Not all allergists accept this opinion Many reduce the dosage by one third or one half for some patients

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57 | *Emanuel Schwartz*

ADRENOCORTICOSTEROIDS IN THE TREATMENT OF ALLERGIC DISEASES

Cortisone, hydrocortisone, or their analogs and ACTH have afforded satisfactory symptomatic relief in allergic syndromes such as chronic intractable bronchial asthma,[1-15] status asthmaticus, severe seasonal and perennial allergic rhinitis,[16, 17] nasal polyps, allergic dermatoses, drug allergies, serum sickness, Loeffler's syndrome, and occasionally the collagen diseases.[18, 19] Before the administration of the adrenocorticosteroids in the treatment of allergic diseases, the clinician should have an understanding of the physiochemical aspects of adrenocorticosteroids, their effect on allergic tissue responses, and a knowledge of the indications, contraindications, precautionary measures, and side effects.

PHYSIOCHEMICAL ASPECTS OF ADRENOCORTICOSTEROIDS

Since the advent of cortisone, many investigators have attempted to develop new adrenocorticosteroids which possess greater biologic activity and maintain an adequate ratio of glucocorticoid to mineralocorticoid activity. Intensive investigation by chemists in a relatively short period of time has resulted in the discovery of newer and better adrenocorticosteroids.[2-8] Alterations in the chemical configurations of the steroid nucleus and/or its side chains produced cortisone, hydrocortisone, prednisone, prednisolone, methylprednisolone, triamcinolone, and dexamethasone. It has been possible to

correlate physiologic and pharmacologic activity of the adreno corticosteroids or their analogs with their chemical structure [7]

Approximately thirty hormones have been isolated from the adrenal cortex of animals All have an intact steroid or cyclopentanoperhydrophenanthrene nucleus

Six of them are capable of maintaining life in adrenalectomized animals DOC or 11 desoxycorticosterone Compound A or dehydro corticosterone Compound B or corticosterone Compound E or cortisone Compound F or hydrocortisone and Aldosterone The six compounds have the following common characteristics (*a*) A double bond appearing between carbons 4 and 5 in ring A (*b*) A double bonded oxygen atom at carbon 3 of ring A (*c*) Oxygen at carbon 20 (*d*) A hydroxyl group at carbon 21 appearing as CH OH (Fig 57 1)

The chemical characteristics common to all biologically active adrenocorticosteroids is the formula of desoxycorticosterone Four of the six adrenocorticosteroids that possess biologic activity are useful clinically namely *desoxycorticosterone* aldosterone cortisone and hydrocortisone Desoxycorticosterone and aldosterone have been designated as mineralocorticoids Because of their marked mineralocorticoid activity lack of effect on the intermediate metabolism of carbohydrates and absence of anti inflammatory and antiallergic activity they are ineffective and contraindicted in allergic diseases

Compounds characterized by oxygenation at C 11 have been designated as glucocorticoids and are associated with reduced or moderate mineralocorticoid activity and moderate carbohydrate effect i e Compound A and Compound B The addition of a hydroxyl group at C-17 to Compound A and Compound B forms cortisone and hydrocortisone respectively Cortisone and hydrocortisone are associated with weak sodium retaining effect strong carbohydrate regulating potency and anti inflammatory and antiallergic effect The anti inflammatory and antiallergic activity usually parallels the glucocorticoid activity Compound A and Compound B do not possess a hydroxyl group at C 17 and thus are not associated with anti inflammatory or antiallergic activity They are not useful in the treatment of allergic diseases Cortisone and hydrocortisone because of their anti inflammatory and antiallergic effects and a reasonable maintenance of an adequate ratio of glucocorticoid to mineralocorticoid activity have afforded satisfactory symptomatic relief in allergic diseases Although symptomatic relief was almost invariably more gratifying than had hitherto been obtained with other methods of treatment it was complicated by adverse side effects

Chemists continued their attempts to develop new compounds

to produce greater potency and at the same time to decrease the severity and number of side effects Newer and better adrenocorticosteroids were developed and in animal studies it was shown that they possessed a high degree of glucocorticoid activity as evidenced by thymus involution liver glycogen deposition eosinophil depletion decreased mineralocorticoid activity and increased anti inflammatory activity (granuloma inhibition)

The substitution of a hydroxyl group for the oxygen atom at C 11 in the cortisone structural formula resulted in hydrocortisone Dehydrogenation of cortisone and hydrocortisone or the addition of a double bond in ring A at carbons 1 and 2 to the cortisone and hydrocortisone structures resulted in prednisone and prednisolone respectively increasing their potency three to five times It was also shown that the 11 beta hydroxyl substituted steroids such as hydrocortisone and prednisolone showed slightly greater potency than the 11 ketone group steroids such as cortisone and prednisone In addition to increased potency prednisone and prednisolone were also associated with decreased mineralocorticoid activity in therapeutically effective doses The introduction of a flourine atom into the hydrocortisone structural formula at the C 9 alpha position resulted in 9 alpha fluorohydrocortisone with increased glucocorticoid and antiinflammatory activity to several times that of hydrocortisone However it also increased the mineralocorticoid activity several times that of desoxycorticosterone Applied topically it is useful in the treatment of allergic dermatoses but because of the production of edema when administered orally it is contraindicated in allergic diseases

Further alterations in the chemical configurations in the steroid nucleus and/or its side chains produced methylprednisolone triamcinolone and dexamethasone In triamcinolone 16 alpha hydroxylation markedly decreased the mineralocorticoid activity and abolished the sodium retaining properties of 9 alpha flurosteroids without destroying their glucocorticoid activity It is one and a half to two times more potent than prednisolone The substitution of 16 alpha methyl group for a 16 alpha hydroxy in the 9 alpha fluoroprednisolone formula formed dexamethasone and resulted in even greater therapeutic activity Dexamethasone is seven to ten times more potent that prednisolone The greater therapeutic activity of triamcinolone and dexamethasone is not accompanied by a corresponding increase in the production of adverse effects The evolution and chemical structures of the above adrenocorticosteroids and their analogs are illustrated in Fig 57 1

A list of adrenocorticosteroids used in allergic disease is shown in Table 50 at the conclusion of this chapter

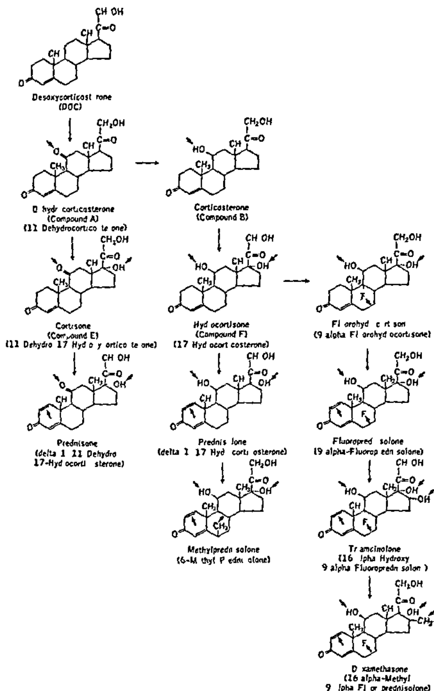


Fig 57 1 Evolution and chemical structures of adrenocorticosteroids and their analogs The shaded areas show successive changes from the progenitor Desoxycorticosterone

Tissue cells require adrenocorticosteroids for their normal function Approximately 25 mg of cortisone and 1 to 2 mg of desoxycorticosterone are secreted from the adrenal cortex in twenty four hours [60] During stress increased quantities are necessary and in response

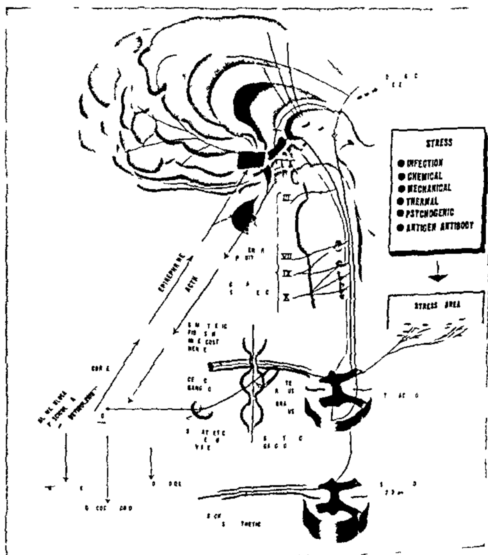


Fig 57 2 Physiologic regulation of adrenal cortical secretion

approximately 100 mg of cortisone is secreted by the adrenal cortex. The physiologic regulation of adrenal cortical secretion is controlled by the hypothalamus pituitary adrenal hormonal system When exposed to stress the hypothalamus pituitary adrenal mech

anism can be rapidly activated from the stress area through the sympathetic to adrenal medulla resulting in release of epinephrine Epinephrine reaches the hypothalamus via the systemic circulation causing a release of a hormonal substance from the hypothalamus which stimulates the anterior pituitary This causes a release of corticotropin which stimulates the adrenal cortex to release corticosteroids Activation through the sympathetic is of short duration The regulation of adrenal cortical secretion can be maintained over a long period by activation of the anterior pituitary from the stress area through the higher brain centers and the hypothalamic nuclei (Fig 57 2)

Corticotropin is also secreted in response to a decreased level of circulating adrenocorticosteroids Adrenal cortical activity results in the secretion of desoxycorticosterone from the *zona glomerulosa* or outer layer whose main physiologic activity is to regulate the distribution and excretion of sodium and potassium and to regulate water balance Estrogen androgen and progesterone are secreted from the *zona reticulosa* or inner layer and hydrocortisone and probably aldosterone from the middle layer or *zona fasciculata*

Administration of adrenocorticosteroids suppresses ACTH secretion and thereby reduces adrenal cortical activity prolonged therapy or large doses may produce an atrophy of the adrenal cortex and an atrophy of the anterior pituitary If the adrenocorticosteroid is discontinued both slowly return to normal and even at six months they may not yet be quite normal [8] There is no evidence that prolonged steroid therapy produces irreversible suppression of adrenocortical function [9] Small doses or short term therapy with ACTH may produce an atrophy of the anterior pituitary and large doses or prolonged therapy with ACTH may also produce a hypertrophy of the adrenal cortex in addition to atrophy of the anterior pituitary If ACTH is discontinued the adrenal cortex atrophies because of the atrophy of the anterior pituitary and both slowly return to normal

EFFECT OF ADRENOCORTICOSTEROIDS ON ALLERGIC MECHANISMS

Adrenocorticosteroids suppress the clinical manifestations of allergic diseases and afford symptomatic relief The union of antigen and antibody acts as a stress and either alone or with other stressing stimuli such as infection or psychogenic disturbances causes a liberation of histamine acetylcholine serotonin and unknown substances which trigger allergic tissue responses The exact mode of action of the adrenocorticosteroids is not clearly understood It is

suggested that they act locally upon the sensitized tissue cells[30] decrease the reactivity of the shock organs to specific antigens and/or stress and suppress local tissue responses rendering the cells less subject to injury They decrease capillary permeability and prevent formation of edema and granulation tissue They decrease circulating eosinophils and lymphocytes In allergic diseases the ground substance of the mesenchymal connective tissue is edematous and stains lightly Rappaport[31] attributes this to a breakdown of the mucoproteins comprising the ground substance The adrenocorticosteroids decrease edema increase the stainability of the ground substance and restore the thickness and stainability of the basement membrane This was interpreted as caused by the arrest of mucoprotein breakdown and restoration of the normal state

The output of gluco corticoids and 17 ketosteroids is decreased in many asthmatic patients which suggests that there may be interference or blocking of the normal hypothalamus pituitary adrenal secreting mechanism or an inability of the adrenal cortex to secrete the increased amount of corticosteroids necessary during stress

The adrenocorticosteroids do not alter the hypersensitive state nor is anaphylactic shock prevented in the guinea pig[3] The delayed response of adrenocorticosteroids at local tissue sites will not prevent severe immediate anaphylaxis nor affect it Antigenicity is not decreased and protein synthesis is unaltered[33] In large doses the steroids may suppress[3-34] but do not abolish antibody formation[35, 36, 50–53] They do not cause liberation of antibodies from lymphoid tissue[3] and do not prevent the antigen antibody union[3, 34] With therapeutically effective doses they do not alter allergic skin wheals[38] large dosages however may reduce them[30] They do not alter the nasal and conjunctival tests[38] reagin titre[39] and blocking antibodies[39] or passive transfer tests[40] They do not block the action of histamine and will not prevent histamine shock or alter histamine skin wheals[38, 41] They may in high doses inhibit patch tests[42] and they may also inhibit the tuberculin reaction[43–45] In animals in large doses they will inhibit or reduce in severity the active *Arthus phenomenon*[46–48] *The Schwartzman phenomenon* is inhibited if ACTH is given before the intravenous provocative dose of toxin[49] large doses of cortisone given before the initial dose of toxin may even enhance it[35]

RECOMMENDATIONS AND PRECAUTIONS

Although the relative potencies of the cordicosteroids have been determined in animals a disparity may exist in human subjects

and comparative therapeutic activity with several adrenocorticosteroids was evaluated clinically in allergic diseases in the study below

The results obtained in the symptomatic relief of allergic diseases with adrenocorticosteroids far surpass those previously obtained with any other agent or procedure However adrenocorticosteroid therapy is not a substitute for specific treatment and should be administered as a supplement to immunologic management and other well established symptomatic measures The beneficial effects are suppressive and not curative Because of the possible occurrence of side effects the steroids are not advocated in the routine treatment of allergic patients if satisfactory relief can be obtained by elimination of offending substances hyposensitization and other drugs which are known to give satisfactory symptomatic relief If the severity and the disability of the allergic state i e in status asthmaticus or chronic intractable bronchial asthma outweigh the potential risks of hypocorticism steroid therapy may be considered If the administration of adrenocorticosteroids is indicated short term therapy with the smallest possible maintenance dose for relief is desirable in order to decrease the number and severity of side effects (see also Chap 34)

The best results with the steroids are obtained in self limited diseases such as penicillin and other drug reactions in which with proper dosage and adequate duration of therapy relapses do not occur Steroid therapy also affords moderate to marked relief during acute exacerbations of chronic allergic diseases if adequate dosage is given and sustained during the acute phase In most patients with chronic allergic disease however although relief of symptoms is adequate and at times remarkable it is confined to the period during and immediately following the administration of the steroid After hormone therapy is discontinued symptoms usually return within several hours to several weeks The relief of symptoms is more complete and is maintained for longer periods with relatively small doses of prednisone prednisolone methyl prednisolone triamcinolone and dexamethasone

In hay fever oral hormone therapy combined with hyposensitization and antihistamines produces much greater relief than that obtained with any other treatment However it should be used in selected cases i e in those patients who have marked symptoms during the height of the season and after the usual measures such as hyposensitization and antihistamines have failed

In patients with status asthmaticus epinephrine used frequently usually becomes ineffective and intravenous aminophylline may be of

little or no benefit The early use of adrenocorticosteroids and ACTH is therefore indicated in these cases and gives satisfactory relief in most instances Emergency steroid therapy is indicated in some of these cases where life is threatened (see also Chap 61) The following are the measures which I have found to be of most value in the treatment of status asthmaticus intravenous administration of 33 4 to 50 mg of the sodium salt of prednisolone 21 hemisuccinate in 2 cc of sterile water over a period of approximately one minute or the intravenous administration of 100 mg of the sodium salt of hydrocortisone 21 hemisuccinate in 2 cc of sterile water With intravenous prednisolone there is less chance of sodium retention and the administration can be repeated every 24 hours for two to three days if necessary The addition of prednisolone to large volumes of infusion fluid for administration as a slow intravenous drip is not recommended because of its limited chemical stability in solution Prednisolone should always be used within 30 minutes of its preparation Intravenous prednisolone or hydrocortisone is more rapid in onset of effect than intravenous ACTH There is also the possibility in some of these patients that the adrenal cortex maybe unable to respond to stimulation by ACTH and the increased amount of corticosteroids necessary for the tissues during stress may not be forthcoming from the adrenal cortex

Immediately after the initial intravenous prednisolone or hydrocortisone the treatment can be fortified by an intravenous infusion of 1 000 cc of 5 per cent glucose in water to which 20 units of ACTH 0 5 Gm aminophylline and 0 5 Gm sodium amytal are added This infusion should be extended over a period of 8 to 12 hours and may be repeated in 12 to 24 hours in doses ranging from 10 to 20 units of ACTH with or without aminophylline and/or sodium amytal as indicated until the symptoms are brought under control Sustained adrenocortical stimulation is produced in most patients by small doses of ACTH given by slow intravenous drip The adrenal stimulation depends to a great extent on the duration of administration rather than on the amount of ACTH given Maximal stimulation in the eight hour period is obtained with 20 units of ACTH

After the acute phase has subsided and the symptoms are under control one may change to oral prednisone prednisolone methyl prednisolone triamcinolone or dexamethasone With definite improvement the dosage can be gradually reduced If the patient had chronic intractable bronchial asthma previous to the onset of status asthmaticus prolonged therapy with steroids may be necessary to maintain the symptomatic relief

Once hormone therapy is established the usual therapeutic measures should also be instituted (see Chap 26) Patients who have been epinephrine fast or who have failed to respond to aminophylline previous to hormone therapy will usually respond to these drugs once relief has begun with the steroids

When the relief of symptoms has been well established the therapeutic measures can be gradually discontinued After the dose of the steroid has been tapered off it may be possible for a time to eliminate hormone therapy entirely relief may then be maintained by the usual therapeutic measures

In the treatment of allergic diseases with therapeutically effective doses of adrenocorticosteroids dangerous side effects are seldom encountered However these drugs are extremely potent and precautionary measures are necessary to eliminate side effects or to decrease their number and/or severity These measures were used as a guide in studies undertaken to determine the therapeutic effects of several adrenocorticosteroids in allergic diseases as reported below

Contraindications The corticosteroids were only used when well established methods of treatment such as elimination of offending allergens hyposensitization and the usual symptomatic measures had failed The following conditions generally constituted contraindications to the use of the steroids Cushing s syndrome hirsutism diabetes mellitus peptic ulcer gastrointestinal bleeding tuberculosis psychosis osteoporosis thromboembolic phenomenon chronic renal disease congestive heart failure and significant hypertension However these contraindications were more relative than absolute The decision to use steroids depended on the severity of the allergic manifestations compared to the severity of the complicated disease and the potential risk of hypercorticism If the allergic disease did not respond to other measures and outweighed the severity of the complicated disease and the risk of hypercorticism as was the case with several patients in this study adrenocorticosteroids were given

The preventive measures included frequent clinical observation to determine symptomatic response and the possible presence of adverse effects and the adjustment of dosage Awareness at all times of the possible appearance of the symptoms and signs of the common side effects served as a precautionary measure Some of the adverse effects looked for were hirsutism fullness of face or moon facies fat pads striae acne pigmentation and other signs of Cushing s syndrome gastrointestinal symptoms gastrointestinal bleeding fluid retention psychic disturbances potassium deficiency osteoporosis thromboembolic phenomenon ecchymosis muscular weak

ness activation of infection and withdrawal symptoms caused by adrenal cortical hypofunction

Clinical observation and follow up studies included a regular physical examination the weight of the patient blood pressure determinations and urinalysis for sugar before and during treatment With large doses of the steroids or in known diabetes the urine was examined daily and with small doses once weekly Pretreatment x rays of the chest were obtained and on prolonged therapy were repeated every three months Pretreatment x rays of the spine were also obtained in several patients and were repeated every three months *when osteoporosis* was present and more *frequently when* there were fractures With long term therapy in uncomplicated cases x rays of the spine were obtained every six months

Adrenocorticosteroids may mask the signs and symptoms of infection Patients were therefore examined frequently and carefully for the presence of infection and when present supplementary antibiotics were administered in larger doses than is usually indicated Adrenocorticosteroids may also interfere with the defence mechanism to infection They should not be administered in the presence of infection *without the protection of a potent antibiotic* Likewise corticosteroids should not be used in the presence of resistant organisms or in fungal or viral infections

Upon discontinuation of the steroids or on a too rapid decrease in dosage several patients complained to tiring easily weakness nervousness irritability gastrointestinal disturbances and sometimes dizziness These withdrawal symptoms were treated by (1) increasing the dose of the steroid and then decreasing the dose once more but more slowly every four to seven days (2) giving ACTH for several days or (3) both of these methods In some cases the adrenal cortex may not respond to ACTH and here the block lies at the pituitary rather than the adrenal cortical level

Appearance of muscular weakness fatigue restlessness or sweating was further investigated as possible symptoms of hypopotassemia by taking electrocardiographic tracings and performing blood potassium determinations When hypopotassemia was demonstrable a daily dose of 3 to 5 Gm of potassium chloride and one glass of orange juice were given

During stress, i e preoperatively and postoperatively or following *an accident the dose of the steroid was increased Steroids* should be administered preoperatively and postoperatively even to those patients who had received small doses for a few days within six months prior to surgery If steroids were indicated in allergic disease complicated by tuberculosis antimicrobial therapy was administered if com

plicated by peptic ulcer antacids ulcer diet cholinergic blocking agents and substitution of hydrocortisone for prednisone or prednisolone was usually prescribed More recently in order to decrease the possibility of adverse gastrointestinal effects antacids were administered to all patients on adrenocorticosteroids If complicated by diabetes the insulin requirements were adjusted If osteoporosis is present *steroids should be discontinued if possible If the severity* of the allergic disease outweighs the severity of the adverse effect steroids should be given with a high protein diet male and female sex hormones calcium and vitamin D

CLINICAL EVALUATION OF ADRENOCORTICOSTEROIDS IN ALLERGIC DISEASES

In 1950 a study was undertaken to determine the therapeutic effects of cortisone in patients with allergic diseases As newer and better adrenocorticosteroids were discovered and made available *they were investigated clinically Thus hydrocortisone prednisone* prednisolone methylprednisolone triamcinolone and dexamethasone have been evaluated in the symptomatic relief of allergic patients The patients in this study were either from private practice or from the Allergy Clinic of The Long Island College Hospital This afforded an opportunity for comparative studies of the symptomatic relief and occurrences and severity of side effects with these steroids and also comparative studies between short term and prolonged continuous therapy The term *short term* was applied to all patients on relatively small doses of adrenocorticosteroids up to nine months This was done in order to compare this group with another one receiving prolonged therapy over a period of two to eight years It is fully realized that steroid therapy longer than two to three weeks may be considered by others as prolonged therapy

The symptomatic relief obtained with cortisone and/or hydrocortisone was superior to that obtained with any other previous agent or procedure However with the discovery of prednisone prednisolone[64] [55] methyl prednisolone[56] [57] *triamcinolone* [9] *and dexamethasone* [26] the therapeutic activity increased and recently clinical evaluation in allergic diseases was concentrated on the newer adrenocorticosteroids

SHORT TERM THERAPY

Prednisone and Prednisolone There were 345 patients in this group A total of 163 patients received prednisone and 182 received prednisolone Prednisone and prednisolone were found to be in

terchangeable because the degree of symptomatic relief and the occurrence and severity of side effects were approximately similar with both drugs Statistically they have been grouped together The duration of treatment was from three days to six months

Prednisone and prednisolone were administered orally and the total daily dose was divided into four doses given at mealtime and before bedtime The proper dose was the smallest amount necessary to produce the desired symptomatic relief In this series the initial daily dose usually ranged from 15 to 20 mg and the maintenance dose was usually from 10 to 15 mg daily In several patients a maintenance daily dose as low as from 2 5 to 7 5 mg controlled symptoms and in others occasional increases to 25 mg daily were necessary to maintain satisfactory relief Changes in dosage were made every four to seven days by decreasing the daily dose by 2 5 mg to arrive at a satisfactory maintenance dose

Symptomatic relief usually began within 24 hours occasionally after the first or second dose and at times after as long as 48 hours Many of these patients had previously been treated with cortisone and hydrocortisone Relief of symptoms was more complete and was maintained for longer periods with relatively small doses of prednisone or prednisolone Adequate relief was obtained in 189 of 214 patients with bronchial asthma 59 of 68 patients with seasonal allergic rhinitis 15 of 21 patients with nonseasonal allergic rhinitis 6 of 6 patients with acute urticaria 11 of 18 patients with allergic eczema and 10 of 10 patients with contact dermatitis The results of short term therapy with prednisone or prednisolone in allergic diseases are shown in Table 40

TABLE 40 RESULTS OF SHORT TERM TREATMENT WITH PREDNISONE AND PREDNISOLONE IN ALLERGIC DISEASES

Allergic condition	Number of cases	Degree of symptomatic relief			
		Marked	Moderate	Slight	None
Bronchial asthma	214	13	54	17	8
Seasonal allergic rhinitis	68	41	18	3	6
Nonseasonal allergic rhinitis	21	8	7	0	6
Acute urticaria	6	3	3	0	0
Chronic urticaria	8	1	3	1	3
Allergic eczema	18	6	[illegible]	1	6
Contact dermatitis	10	3	[illegible]	0	0
Total	[illegible]	[illegible]	97	[illegible]	[illegible]

Side Reactions For the purpose of comparative studies of the occurrence and severity of side effects the 345 patients receiving prednisone and prednisolone therapy were divided into two groups Sixty eight severe hay fever patients received prednisone or prednisolone from 3 to 44 days with an average of 15 days Side effects occurred in 5 patients or in 7 4 per cent (see Table 41)

TABLE 41 STUDY OF 68 CASES OF HAY FEVER TREATED WITH PREDNISONE AND PREDNISOLONE *

Side reaction †	No of cases
Fullness of face	2
Acne	2
Epigastric distress	1
Total	5

Duration of therapy 3 to 44 days average 15 days
† Occurred in 5 cases (7 4%)

Two hundred and seventy seven patients with miscellaneous allergies excluding those with hay fever received prednisone or prednisolone from three days to six months with an average duration of therapy of four months Side effects occurred in 40 or 14 5 per cent of the patients (see Table 42)

TABLE 42 STUDY OF 277 CASES WITH MISCELLANEOUS ALLERGIC DISEASES TREATED WITH PREDNISONE AND PREDNISOLONE *

Side reaction †	No of cases
Fullness of face	27
Acne	3
Epigastric distress	2
Bloating	1
Insomnia	2
Substernal pain	1
Palpitations	1
Weakness	1
Hypertension (mild)	1
Thrombophlebitis (?)	1
Total	40

Duration of therapy 3 days to 6 months average 4 months
† Occurred in 40 cases (14.5%)

In both groups there was no clinical evidence of any dangerous side effects On discontinuation, or decrease of the dose side effects disappeared or decreased in intensity

Triamcinolone Triamcinolone[59] was administered to 50 selected patients with chronic intractable bronchial asthma over a period of from one to nine months Triamcinolone was selected because animal investigation [9] demonstrated that it had remarkably potent glucocorticoid activity markedly reduced mineralocorticoid activity and minimal occurrence of the usual adverse side effects These patients were selected because all had suffered with chronic intractable bronchial asthma for many years and because previous available therapy (with the exception of steroids) failed to afford symptomatic relief Several of the patients however had previously received other adrenocorticosteroids and this provided an opportunity for comparative studies Triamcinolone was not used to the exclusion of other forms of therapy it supplemented other immunologic and symptomatic management With the institution of triamcinolone therapy other adrenocorticosteroids were discontinued The dosage and therapeutic response are illustrated in Table 43

TABLE 43 THERAPEUTIC RESPONSE TO TRIAMCINOLONE THERAPY IN CHRONIC INTRACTABLE BRONCHIAL ASTHMA

	mg/day	Excellent	Good	Fair
Low maintenance dose 1-4 mg/day 39 cases 1-8 months	4	19	14	1
	3	13		2
	2		1	1
	1	14	14	
		22 Cases	13 Cases	4 Cases
Higher maintenance dose (by three courses) 6-16 mg/day 11 cases 2-9 months	10-16	12	12	
	8		1	
	6		4	
		4 Cases	7 Cases	
Total 50 Cases		26 Cases (52%)	20 Cases (40%)	4 Cases (8%)

In 46 cases (92 per cent) the response was good to excellent In most patients triamcinolone and prednisolone afforded an equal degree of symptomatic relief In some triamcinolone produced better relief and in others prednisolone Smaller doses of triamcinolone were required as a rule for the necessary relief In comparative studies triamcinolone was shown to be one and one half to two

times more potent than prednisolone However most of the adverse reactions encountered with prednisolone were also observed with triamcinolone With triamcinolone several of the patients developed a decrease in appetite and there was a weight loss in five patients Side effects observed in 50 cases are tabulated in Table 44

TABLE 44 STUDY OF 50 CASES OF CHRONIC INTRACTABLE BRONCHIAL ASTHMA TREATED WITH TRIAMCINOLONE *

Side reaction †	No of side reactions
Moon face	1
Tachycardia	1
Nausea pyrosis	1
Bloating	1
Sweating flushing	1
Weakness	2
Fatigue	1
Acne	1
Hirsutism	1 ‡
Striae	1 ‡

Duration of therapy 1 to 9 months
† Occurred in 9 cases (18%)
‡ Result of previous steroid therapy

Triamcinolone is a useful drug in the management of chronic intractable asthma because of the satisfactory symptomatic relief obtained with comparatively small doses the relative infrequency of adverse side effects and the absence of severe side effects with short term therapy

6 Methyl Prednisolone Methylprednisolone was found to be equally as or slightly more potent than prednisolone and the number and severity of side reactions were either approximately the same or slightly fewer with methylprednisolone [56, 57] In my limited experience comparative doses with prednisolone have shown that the two adrenocorticosteroids possess equal antiallergic activity and the frequency and severity of side effects did not differ significantly with short term therapy

Dexamethasone Dexamethasone or 16 alpha methyl 9 alpha fluoroprednisolone is a new adrenocorticosteroid with an increased therapeutic index as compared to other steroids Studies in rats [5, 6] disclosed the fact that dexamethasone was 190 times more potent than hydrocortisone in inhibiting granuloma formation and 17 times more active in promoting glycogen deposition Dexamethasone to date is the most potent anti inflammatory steroid and in the adrenalectomized rat produced neither sodium retention nor increased

potassium excretion Comparative studies with other adrenocorticosteroids have shown that for the first time a steroid was synthesized with significant disparity between its anti inflammatory potency and glucocorticoid activity

TABLE 45 RESULTS OF TREATMENT WITH DEXAMETHASONE IN ALLERGIC DISEASES

Allergic condition	Number	Degree of symptomatic relief: Good Excellent	Fair	None
Bronchial asthma	36	32	2	2
Seasonal allergic rhinitis	8	7	0	1
Nonseasonal allergic rhinitis	7	7	0	0
Chronic urticaria	2	1	0	1
Contact dermatitis	2	2	0	0
Nasal polyps	2	2	0	0
Total	57	51	2	4

Dexamethasone was administered to 51 patients with 57 allergic conditions over a period of from one week to four months The initial daily dose ranged from 0 4 mg to 3 2 mg and the daily maintenance dose from 0 4 to 2 0 mg The symptomatic relief was good to excellent in 51 of 57 allergic conditions The therapeutic response is illustrated in Table 45 Fourteen side effects occurred in 9 of 51 patients and are illustrated in Table 46 With a decrease of dosage toward the end of the day and proper spacing insomnia disappeared in one patient The other patient who had insomnia and also purpuric spots had to discontinue the medication because of insomnia For several days an attempt was made to decrease the dose with proper spacing to eliminate the insomnia but the optimum response was not attained On full maintenance dosage the purpuric spots disappeared Another patient with edema of the ankles and bloating was placed on a low sodium diet and on the same dosage of dexamethasone the edema disappeared and the bloating was less severe No ulcerated areas were visible on the x rays of the stomach and duodenum in this patient and in another patient with substernal pressure Purpura occurring in another patient disappeared although the same dose was maintained A weight gain of 15 lb in one patient and 11 lb in another occurred during four months of medication On decreased dosage a loss of one half of the weight gain occurred in both patients In two of the patients in this series who suffered

from diabetes mellitus dexamethasone therapy did not cause any increase in the insulin requirement

TABLE 46 STUDY OF 51 CASES OF ALLERGIC DISEASE TREATED WITH DEXAMETHASONE *

Side reaction †	No of side reactions
Fullness of face	4
Insomnia	2
Weakness	1
Bloating	2
Substernal pressure	2
Purpura	2
Edema	1
Total	14

Duration of therapy 7 days to 4 months
† Occurred in 9 cases (17 6%)

Dexamethasone is a useful drug in allergic diseases because satisfactory relief was obtained in over 90 per cent of the patients A greater degree of symptomatic relief was obtained in approximately one fourth to one third of the patients on dexamethasone in comparative studies with triamcinolone and prednisolone It was seven to ten times more potent than prednisolone and four to five or six times more potent than triamcinolone The increased potency of dexamethasone is not accompanied by a corresponding increase in the number and severity of adverse effects

PROLONGED CONTINUOUS THERAPY

Thirty five patients comprised this group Thirty two had chronic intractable bronchial asthma two had severe perennial allergic rhinitis and one had allergic eczema Prolonged continuous therapy was administered over a period of two to eight years with an average of three years and seven months (see Table 47) With many of these patients treatment was first started with cortisone and then continued with hydrocortisone prednisone or prednisolone After treatment was transferred to prednisone or prednisolone relief was more complete and adequate improvement was sustained in all In this group the severity of the allergic state and the resulting disability outweighed the potential risks of adreno

corticoid therapy Many attempts were made to decrease the maintenance dose or at times to discontinue steroids entirely only to have the symptoms return It was then necessary to give a larger dose for a few days to obtain the same degree of relief as previously The dose was then gradually decreased to the original maintenance dose once relief again set in Prolonged intermittent therapy was attempted without success and because of the severity of the allergic state prolonged continuous treatment with adrenocorticosteroids was necessary

With prolonged continuous therapy the number and severity of side effects increased Thirty two side effects occurred in 19 patients or 54 per cent of the cases (see Table 48) One patient died because of an overwhelming spread of infection after she had been receiving prednisone or prednisolone for over two years Rapid shock set in and death occurred in 12 hours Autopsy revealed the following pathological findings broncho pneumonia acute interstitial myocarditis atrophy of the cortex of the adrenal gland cytoplasmic degranulation and vacuolization of the basophiles of the anterior pituitary hyalinization of the basement membrane of the bronchioles swollen epithelial cells emphysema and the presence of many eosinophils

TABLE 47 PROLONGED THERAPY WITH ADRENOCORTICOSTEROIDS IN ALLERGIC DISEASES OVER A PERIOD OF TWO TO EIGHT YEARS

Duration of therapy	No of cases
2 to 3 years	16
3 to 4 years	6
4 to 5 years	7
5 to 6 years	3
6 to 7 years	1
7 to 8 years	2
Total	35

One patient with chronic intractable bronchial asthma complicated by pulmonary productive changes caused by tuberculosis was treated with steroids and in addition dihydrostreptomycin and isoniazid there was considerable symptomatic relief of the asthma and no reactivation of the pulmonary lesions

Another patient whose x rays showed osteoporosis and fracture of the right lower ramus of the pelvis after one year of cortisone

therapy was continued on hydrocortisone prednisone and prednisolone therapy for another seven years and has recently shown a slight increase in mineralization and density of bone Both ovaries had been removed six months before the onset of cortisone therapy After six years of steroid therapy including two years treatment with prednisone or prednisolone this patient had an acute anterior myocardial infarction The infarction healed although steroid therapy had been continued

Table 48 Study of 35 Cases of Allergic Disease with Prolonged Adrenocorticosteroid Therapy *

Side reaction †	No of side reactions
Fullness of face	9
Glycosuria	3
Increase in glycosuria (in diabetes mellitus)	2
Overwhelming spread of infection	1
Gastrointestinal bleeding	1
Osteoporosis	1
Weakness	2
Bloating	3
Abdominal wall edema	1
Acne	1
Striae	1
Palpitations	2
Nervousness	1
Diuresis	2
Sweating	1
Increase in hirsutism	1
Total	3[illegible]

* Duration of therapy 2 to 8 years average 3 years 7 months
† Occurred in 19 cases (54%)

Another patient had had eight or ten attacks of thrombophlebitis previous to steroid therapy and developed another two attacks of thrombophlebitis one during hydrocortisone therapy and one after two months of predisolone therapy There has been no recurrence of thrombophlebitis during the last sixteen months of prednisolone medication

One patient with bronchial asthma complicated by aortic stenosis congestive heart failure and a hiatus hernia died and autopsy showed marked calcification of the aortic valve congestive heart

failure and no evidence of bleeding because of the hiatus hernia Three weeks previously gastrointestinal bleeding had been present and although steroids were continued there was no evidence of bleeding at autopsy

In an asthmatic patient with bilateral nasal polyps the polyps decreased markedly in size and shrinkage was maintained for two years on 10 to 20 mg of prednisone or prednisolone daily

The comparative effects of prolonged therapy with cortisone hydrocortisone prednisone and prednisolone in several cases of severe intractable bronchial asthma are shown in Table 49

TABLE 49 COMPARATIVE EFFECTS OF PROLONGED THERAPY WITH CORTISONE HYDROCORTISONE PREDNISONE AND PREDNISOLONE IN FIVE CASES OF SEVERE INTRACTABLE ASTHMA

	Duration of therapy	Results	Side reactions
Case 1—F age 38 asthma 4 years			
Cortisone	1½ years	Moderate relief	Osteoporosis
Hydrocortisone	2½ years	Moderate relief	Osteoporosis unchanged substernal pain EKG normal
Prednisone	1 year	Excellent relief	Osteoporosis unchanged substernal pain EKG normal
	2 years	*Excellent relief*	*Osteoporosis unchanged* no substernal pain for first 18 months EKG showed anterior infarction
Total	7 years		
Comment Anterior infarction occurred but healed while prednisolone therapy continued			
Case 2—M age 50 asthma 6 years			
Cortisone	1 month	No relief	None
Hydrocortisone	2½ years	Marked relief	Bloating
Prednisone	6 months	Excellent relief	None
Prednisolone	2 years 2 months	Excellent relief	None
Total	5 years 5 months		
Comment No relief from ACTH No relief from cortisone Marked relief with hydrocortisone Excellent relief with prednisone and prednisolone			
Case 3—F age 44 asthma 6 years			
Cortisone	2 months	No relief	Palpitation nervousness
Hydrocortisone	2 years 8 months	Moderate relief	Fullness of face

TABLE 49 COMPARATIVE EFFECTS OF PROLONGED THERAPY WITH CORTISONE HYDROCORTISONE PREDNISONE AND PREDNISOLONE IN FIVE CASES OF SEVERE INTRACTABLE ASTHMA (*Continued*)

	Duration of therapy	Results	Side reactions
Case 3—F age 44 asthma 6 years			
Prednisone	2 months	Marked relief	Fullness of face less than with cortisone
Prednisolone	16 months	Marked relief	Fullness of face less than with cortisone same as with prednisone patient asymptomatic after 4 months without steroids
Total	4 years 4 months		
Comment Corticosteroids continued during shock caused by ruptured colon due to auto accident Recovery good Wound healing not delayed			
Case 4—F age 5 asthma 4 years			
Cortisone	1 year	Slight relief	Increased insulin requirement epinephrine requirement 5 to 15 injections daily
Hydrocortisone	3 months	Moderate relief	Insulin requirement less epinephrine requirement 2 to 3 injections daily thrombophlebitis
Prednisone	6 months	Marked relief	No epinephrine insulin requirement less
Prednisolone	2 years 4 months	Marked relief	No epinephrine insulin requirement less thrombophlebitis
Total	4 years 3 months		
Case 5—M age 27 asthma 1 years			
Hydrocortisone	18 months	Slight relief	Fullness of face
Prednisone	2 months	Marked relief	Fullness of face same as with hydrocortisone acne
Prednisolone	2 years 7 months	Marked relief	Fullness of face same as with hydrocortisone and prednisone acne striae
Total	4 years 3 months		
Comment No exacerbation of previous psychosis with corticosteroid therapy			

To facilitate the proper use of the steroids they are listed in Table 50 along with the trade name manufacturer and dosage forms available

TABLE 50 ADRENOCORTICOSTEROIDS USEFUL IN ALLERGIC DISEASES

Generic and chemical name	Principle trade name and manufacturer	Principal forms and dosage
Cortisone (11 dehydro 17 hydroxy corticosterone Compound E)	Cortone (Merk Sharp & Dohme)	Tablet 25 mg Injectable I M 25 mg /1 cc Ointment 1% 2.5% Eye drops 0.5% 2.5%
	Cortogen (Schering)	Tablet 5 mg 25 mg
	Cortisone Acetate (Upjohn)	Tablet 5 mg 25 mg
Hydrocortisone (17 hydroxycortico sterone Compound F)	Hydrocortone (Merk Sharp & Dohme)	Tablet 10 mg 20 mg Ointment 1% 2.5% Dental ointment 1% 2.5% Eye drops 0 5% 2.5% Injectable 20 mg /1 cc
	Cortril (Pfizer)	Tablet 10 mg 20 mg Ointment 1% 2.5%
	Cortifan (Schering)	Ointment 1%
	Cortef (Upjohn)	Tablet 10 mg 20 mg Ointment 1% 2.5% Injectable (Solucortef) 100 mg /1 cc
Prednisone (delta 1 11 dehydro 17 hydroxycorticosterone)	Meticorten (Schering)	Tablet 1 mg 2.5 mg 5 mg
	Deltra (Merk Sharp & Dohme)	Tablet 2 5 mg 5 mg
Prednisolone (delta 1 17 hydroxy corticosterone)	Meticortelone (Schering)	Tablet 1 mg 2.5 mg 5 mg Injectable 25 mg /1 cc Hemisuccinate I V 50 mg /1 cc Ointment Metiderm 0.5%
	Hydeltra (Merk Sharp & Dohme)	Tablet 1 mg 2.5 mg 5 mg
	Sterane (Pfizer)	Tablet 1 mg 2.5 mg 5 mg
	Delta Cortef (Upjohn)	Tablet 1 mg 2.5 mg 5 mg
Fluorohydrocortisone (9 alpha fluorohydro cortisone)	Fluorohydrocortisone (Squibb)	Ointment 0 1% 0 2%
6 Methyl prednisolone (6 alpha methylpred nisolone)	Medrol (Upjohn)	Tablet 2 mg 4 mg
Triamcinolone (16 alpha hydroxy 9 alpha fluoroprednisolone)	Aristocort (Lederle)	Tablet 2 mg 4 mg
	Kenacort (Squibb)	Tablet 2 mg 4 mg
Dexamethasone (16 alpha methyl 9 alpha fluoroprednisolone)	Decadron (Merck Sharp & Dohme)	Tablet 0 4 mg 0.5 mg
	Deronil (Schering)	Tablet 0 4 mg

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Frederick R Brown | 58

ANTIHISTAMINIC DRUGS IN THE TREATMENT OF ALLERGIC DISEASES

It has been generally accepted that histamine plays an important role in the allergic reaction When allergen and allergic antibody combine histamine or a similar substance is released producing its physiologic effects on the organism There are four major methods used to prevent allergic reactions (1) elimination or avoidance of the allergen (2) specific hyposensitization by means of allergenic extracts (3) suppression of the action of histamine by means of antihistamines and (4) inhibition of the allergic reaction by means of steroid therapy

After years of search for substances antagonistic to the action of histamine Fourneau and Bovet reported that certain phenolic ethers had this property The early antihistamines proved too toxic for human use but since that time many different types of compounds have been found to have antihistaminic effects without undue toxicity

The chief action of antihistamines is to compete with released histamine at its site of action preventing its effect on the receptor cells Experimentally the antihistamines have been found to prevent histamine and anaphylactic shock in animals inhibit experimental induction of asthma in guinea pigs by histamine aerosols inhibit wheal and flare produced by histamine prevent histamine contraction of smooth muscle in vitro and act as local anesthetics

RESPIRATORY ALLERGY

The best results of antihistamine therapy are obtained in seasonal hay fever Relief is most pronounced in the edematous phases of the illness sneezing rhinorrhea and itching When nasal obstruction is present much less relief is obtained and often patients note that the drying effect increases their nasal obstruction Antihistamine therapy produces greatest relief at the beginning of the season when the symptoms are mildest in the later part of the season when symptoms are more severe the relief obtained is less complete The use of antihistamines is no substitute for specific hyposensitization with pollen extracts Those patients receiving pollen therapy usually note that their attacks of hay fever are considerably milder and the use of antihistamines during the season may complete the therapy providing excellent relief Occasionally antihistamines may be used to increase the patient s tolerance for pollen dosage either by oral use an hour before an injection or by combination of an injectable form of the drug with the pollen extract This is most useful in those patients very susceptible to systemic reactions after pollen injections but in general one cannot raise dosage significantly by this method

In perennial allergic rhinitis the results of antihistamine therapy are not so good The greater incidence of nasal obstruction and secondary changes due to the more prolonged exposure to both intrinsic and extrinsic factors probably accounts for the difference in response When extrinsic factors are the major cause greater relief is obtained Most patients with nasal allergy have their most prominent symptoms early in the morning and the use of an antihistamine at that time may be all that is necessary Others find that a decrease in symptoms after arising may occur when prolonged action antihistamines or a combination of a regular and a delayed action form of the drug is taken just before retiring In daytime use the beneficial effect of the drug should appear within an hour after administration If no relief is evident and toxic effects are absent the dosage of the drug should be increased or a different type of antihistamine should be tried Occasionally a patient with very resistant symptoms may be helped by a topical antihistamine spray but often this type of local therapy may be irritating and increase sneezing More recently the addition of hydrocortisone to topical spray preparations has improved their effectiveness

In bronchial asthma the response to antihistaminic drugs is poor Those patients who report improvement are benefited subjectively

by reduction of the asthmatic or preasthmatic cough The latter symptom is more frequent in children and responds well to small doses of antihistamines prescribed in elixirs or syrups Administration of the drug to children before retiring produces the best effects and often assures a good night s sleep The antihistamines which produce sedation seem to be more effective in children even in small dosage In adults with frank asthma very little benefit is noticed with no change in dyspnea or wheezing and in many patients the symptoms are aggravated by the drying effect on these drugs on bronchial secretions Symptomatic therapy in adult asthma is much more effective with sympathomimetic drugs Some patients find that they can abort a mild asthmatic attack by taking the drug early An occasional patient will respond better to a combination of an antihistamine with ephedrine or aminophylline than to the bronchodilator drug used alone The antihistamines have no marked effect in pollen asthma which is effectively controlled by hyposensitization

ALLERGIC DERMATOSES

Urticaria Generally the author s best results with antihistamine therapy occur in urticaria primarily due to the antipruritic effect of these drugs When pruritus is relieved and scratching ceases secondary irritation usually disappears and no new lesions due to localized trauma develop There may be only slight effect on the edematous lesions already present but new lesions may be prevented The response of angioedema to these drugs is much less prominent but even here the duration and size of the edematous areas may be reduced The drugs are more effective in acute urticaria than in chronic urticaria The dosage frequently depends on the severity of the lesion often requiring two to four times the usual dose of the antihistamine The highly sedative antihistamines and those with prolonged action are usually more effective in the relief of urticaria One may find it necessary to try several different drugs before effective relief is obtained in these syndromes Topical application of antihistaminic ointments may be effective in localized lesions due to insect bites

Atopic and Contact Dermatitis In atopic dermatitis one often fails to control the symptoms with antihistamine therapy alone Here again the antipruritic action will sometimes allow the lesions to heal and thus aid in discovering the etiologic factors by other means Since steroid ointments topically applied to the lesions are much more effective in this condition the author no longer uses

antihistaminic ointments The latter are frequent causes of sensitization by contact and this factor alone limits their use The sedative and prolonged action antihistamines are preferred in atopic dermatitis particularly since the condition may be a psychosomatic expression in many patients

In contact dermatitis one may use topical preparations of the drugs because the lesions are usually well localized but here also more effective steroid preparations now exist

DRUG ALLERGY

In the serum sickness type of penicillin reaction the antihistamines are useful in controlling the urticarial and edematous lesions but often fail to affect the fever or arthralgia usually present The course of serum sickness is not affected and the drugs are merely palliative Administration of an antihistamine concurrently with penicillin has not proved adequate to prevent either immediate or delayed reactions to the drug in most instances In drug allergies manifested by urticarial lesions the antihistaminic drugs frequently will control and sometimes prevent lesions If another drug can be substituted for the offending drug this should be done in preference to using antihistaminic suppression

MISCELLANEOUS ALLERGIES

In *allergic conjunctivitis* topical antihistamine therapy will often control the pruritic symptoms allowing more rapid healing of the condition but steroid solutions are probably more efficient

For *gastrointestinal allergy* to foods the oral use of an antihistamine prior to the ingestion of the known allergen will sometimes prevent the symptoms but for most patients it is more logical to avoid the suspected food One should prescribe those antihistamines which do not produce gastrointestinal symptoms as side reactions

Mention should be made of the use of antihistamines for the *common cold* We have no good evidence that antihistamines affect either the course or incidence of the common cold although symptoms such as sneezing and rhinorrhea may be relieved It is often difficult to distinguish between infective and allergic rhinitis and those patients who are on prolonged antihistaminic therapy seem to have the same incidence of colds as do nontreated individuals (see Chap 18)

Antihistamines fail to alter effectively the course of the *collagen diseases* The use of antihistamines to prevent *transfusion reactions* is often inadequate to prevent severe symptoms

ADMINISTRATION OF ANTIHISTAMINES

The usefulness of an antihistamine must be evaluated for each individual by comparing the amount of relief obtained with the side effects encountered The antihistamine of choice would be that one which is most effective with the fewest side reactions

The antihistamines tend to fall into three main groups depending on the side reactions produced

Group I These are least potent and least reactive Antistine Neohetramine Theophorin

Group II These are moderately potent and moderately reactive Pyribenzamine Chlor Trimeton Trimeton Diatrin Perazil Histadyl Neo Antergan Tagathen Ambodryl and Clistein

Group III These are highly potent but also highly sedative Benadryl Decapryn and Phenergan

Several of the antihistamines have a prolonged action particularly Perazil and Phenergan Some of the drugs are available in delayed action and repeat action tablets and in a form that is slowly but continually absorbed

Oral administration is the method of choice with antihistamines The dose will vary greatly with each individual and the smallest dose that is effective should be used For nighttime therapy larger doses and prolonged or delayed action forms of the drug may be used If no relief is obtained within an hour of administration the dosage should be increased or another antihistamine tried

Parenteral use of these drugs is rarely necessary but may be resorted to when rapidity of action is desired or there is failure of absorption Topical application in the form of ointments eye drops nasal sprays and aerosols has been previously mentioned

Sometimes a sedative side reaction may be combated by a combination of the antihistamine with ephedrine caffeine or amphetamine Antihistamines can be combined with aminophylline or ephedrine in antiasthmatic preparations but it is doubtful whether the antihistamine adds to the effectiveness of the bronchodilator drug These drugs have been incorporated into expectorant cough mixtures and in this form are quite useful for children

TOXIC REACTIONS

Sedation is the most common side effect This action frequently limits the use of a particular antihistamine during the day The sedative type of antihistamine should be avoided if the patient s work involves fine motions or driving a vehicle

Central nervous system stimulation may be a side reaction with some antihistamines producing such symptoms as irritability ten sion insomnia vertigo and tachycardia Stimulation occurs more frequently when large dosage is used Convulsions have been noted rarely usually in fatal poisoning from these drugs

Gastrointestinal disturbances such as abdominal cramps nausea vomiting and diarrhea are frequently encountered Perazil Pyri benzamine Chlor Trimeton and Diatrin tend to produce this type of toxic reaction and these drugs should be avoided in patients who have a previous history of peptic ulcer or gastrointestinal irritability

Other side effects not infrequently noted are dryness of the mouth urinary retention and palpitation In some patients con tinued use of the drug over a long period results in tolerance with disappearance of side reactions Rarely psychosis has been noted and very rarely bone marrow depression In most instances the side effects cease promptly when the drug is discontinued

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59 | *Samuel J Prigal*

AEROSOL THERAPY IN THE PRACTICE OF ALLERGY

Aerosol therapy has been widely used in the treatment of respiratory diseases It is a form of inhalational therapy a term which also includes the administration of oxygen and other therapeutic gases At times both the aerosol and the gaseous conveyor may serve therapeutic purposes

Although inhalational therapy with steam dates back to earliest recorded medical history aerosol therapy is relatively new The first impetus to this therapy was given by the introduction of a concentrated solution of epinephrine (1 100) for the relief of bronchospasm Since then other bronchodilators have been introduced Then followed the use of chemotherapeutic and antibiotic agents for the control of infection frequently complicating respiratory allergy More recently aerosols of various mucolytic agents have been introduced

Before considering the therapeutic application of these agents the nature of aerosols the rationale of their use and the methods of producing them will be reviewed

NATURE OF AEROSOLS

An aerosol is a suspension of particles solid or liquid in a gaseous phase usually air To be of therapeutic value these particles should range in size from 0 5 to 3 microns In nature aerosols are respon

sible for the colorful sunsets and rainbows mists fogs and smogs In wartime they are used to camouflage warships and to disseminate destructive chemical or bacteriologic agents They are responsible for the radioactive fallout of the A and H bombs On the other hand aerosolization of insecticides and other agents has protected useful vegetation and crops

RATIONALE OF AEROSOL THERAPY

Aerosol therapy affords an opportunity to apply a therapeutic agent directly to the organ in need of treatment Thus epinephrine or other bronchodilators are administered directly to the lung in pulmonary disease Although some of the agents administered as aerosols such as bacitracin affect the respiratory tract primarily or exclusively by topical action most have a combined topical and systemic effect This is true of the bronchodilators and some antibiotics Proof of this is afforded by blood studies following the inhalation of penicillin and streptomycin aerosols in which blood levels were sustained up to six hours after a fifteen minute period of treatment [1] This indicates that the lung acted as a reservoir and slowly released antibiotics into the circulation Evidence for absorption and systemic action of bronchodilators is provided when such symptoms as tachycardia nervousness pallor and temporary elevation of blood pressure follow overdosage with the aerosol

Although in the application of bronchodilators as aerosols the local action may be minor this is not true of the antibiotics and mucolytic agents Indeed some antibiotics such as neomycin polymyxin and bacitracin are deliberately selected for aerosol therapy to produce local action without systemic absorption in order to avoid the systemic toxic reactions which each of these is capable of inducing Not enough is known about the transpulmonary absorption of these antibiotics The author s studies with bacitracin showed only rare instances of absorption via the pulmonary route - Presumably the same behavior applies to the other two antibiotics since no toxic reactions have as yet been reported from inhalation of their aerosols As for the mucolytics they are intended solely for topical action

The topical action of certain agents as aerosols has other advantages Thus it may be possible to administer Terramycin for sinorespiratory infections when oral administration has caused gastro intestinal disturbances Indeed with the aerosol method one can avoid the staphylococcal intoxication which may follow oral antibiotic therapy (As already mentioned however aerosolized peni

cillin and streptomycin have a twofold action local and systemic)

Finally aerosol therapy is a simple method for the self administration of certain drugs particularly the bronchodilators without resorting to costly or painful procedures Many a physician has been spared a night call by the fact that the asthmatic patient may obtain immediate relief from the inhalation of a bronchodilating aerosol

PRODUCTION OF AEROSOLS

Aerosols for therapeutic purposes may be obtained either by breaking down larger particles of liquids or solids or by beginning with exceedingly small particles and building these up to the required size The latter process is used experimentally to produce aerosol particles of uniform size for study The breaking down process involves the use of a variety of forces explosive fire (smoke is a solid aerosol) and propulsive or jet forces delivered by a liquid or gas (including steam) which may then also act as the conveyor Propulsive forces may vary from the simple compression by hand of a rubber ball to the use of bicycle pumps electric pumps compressors etc Most recently freon and similar highly volatile liquids have been used to generate aerosols Housed in a container the volatile liquid is in equilibrium with its gaseous phase under pressure The released gas may be permitted to flow through a nebulizer containing medication (Nebu Halent) More often the therapeutic agent is already in solution and mixed with the freon and when the gas is allowed to escape an effective medicated mist is produced This is the principle of the aerosol bomb Check valves or meters may be added to control the dosage (Medihaler Mistometer) Another method in use in Europe but not yet available commercially in this country utilizes the centripetal force of a spinning wheel to break a liquid into aerosol particles

In addition to the force to break up the particles a nebulizer is needed to produce the mist Nebulizers are of many varieties and capacities but their prime purpose remains the same to contain the *material usually liquid to be aerosolized and to baffle it* so that the larger and therapeutically useless particles are condensed and returned for further aerosolization In Europe elaborate devices are available including those designed for mass treatment[3] In this country until recently aerosol therapy was handicapped by nebulizers of small capacity usually 2 to 5 ml This has led to therapy of short duration with concentrated solutions With the introduction of mucolytic agents with which continuous treatment is advocated

the capacity of the nebulizers has been markedly increased[4] This should lead to improved aerosol therapy

The choice of the nebulizer and the propulsive force (several permutations and combinations are possible) is determined by a number of factors For self treatment the small nebulizer with the hand bulb (De Vilbiss No 40 Vaponephrin etc) is adequate It is best used for the administration of the bronchodilators a few inhalations sufficing The recently introduced Medihaler and Mistometer have provided an effective means of aerosolizing metered doses of epinephrine and isopropylarterenol

For sustained treatment the hand bulb method is too tiring and the nebulizer may be attached to any of the propulsive forces mentioned Oxygen should not be used routinely as a propulsive force since it has no particular advantage over compressed air unless there is anoxemia and oxygen therapy is indicated

The author has used for many years an insecticide sprayer converted into a nebulizer of therapeutic aerosols This apparatus generates steam power to produce the aerosol and therefore has added therapeutic value Because of its relatively large capacity combinations of bronchodilators antibiotics and mucolytic agents may be used

It is not sufficient however just to produce the aerosol It must be delivered to where it can be utilized effectively This raises the question of the durability of aerosols and the use of masks and other devices to enhance aerosol therapy Concerning the stability or durability of a given aerosol it should be pointed out that most materials aerosolized are in aqueous solutions and that the small sized particles produced have a tremendous area for evaporation with the result that the aerosol is very evanescent This instability may not be a deterrent to the treatment of asthma with bronchodilators but is of great importance in the treatment with antibiotics and mucolytic agents and is probably the most important cause of failure of therapy by this method The aerosol just does not last long enough to be therapeutically effective

To overcome the instability of the aerosols the author has used propylene glycol as the principal solvent or vehicle In this way it is even possible to produce long lasting aerosols which may be confined to a tent or closed chamber (bathroom) making it suitable for the treatment of infants and children or for several members of the family simultaneously[6] Propylene glycol has also enabled me to use a primary irritating agent such as Terramycin which in this solution is tolerated but in aqueous solution is not Furthermore

recent studies with propylene glycol reveal that it has mild antihistaminic properties which may account for the absence in my experience of allergic reactions to penicillin aerosol used with propylene glycol

Commonly the patient is treated with an aerosol continuously produced The total production however is much beyond the capacity to consume the patient cannot possibly inhale all that is produced in a given period of time This results in great waste and inefficient therapy To overcome this a demand type of mechanism may be incorporated into the apparatus which limits the production of the aerosol to the period of inhalation only This may be a complicated mechanical device or a simple one in which by means of rubber tubing the propulsive force of the gas may be temporarily shunted away from the nebulizer during exhalation Here by proper timing and coordination aerosol production may be synchronized with inhalation

Fig 59 1 Steam generated aerosols The usual method of aerosolization (1) utilizes compressed oxygen and a nebulizer Steam power even from a vaporizer (2) may be used to produce a mist with a nebulizer In the combined steam generator and aerosolizer (3) no special nebulizer is needed and large volumes may be aerosolized quickly It produces many different sizes of particles some of them too large to be effective For this reason a baffle is added (4) which throws back the larger particles for reaerosolization resulting in a uniform therapeutic mist

Other methods for the more efficient use of aerosols utilize closed systems (chambers tents or masks) so that the mist is not disseminated into the atmosphere A device called by the author a breathing box utilizing a closed system has been previously described and found of particular value in the administration of antibiotics[4] Figure 59 1 illustrates evolution of the steam generator and aerosolizer

CLASSIFICATION OF AEROSOLS

Bronchodilators The first types of aerosol to be introduced and still the most commonly used are the bronchodilators These are epinephrine (1 100) and related substances such as isopropylarterenol (Isuprel Aleudrine) and Vaponephrin a sympathomimetic compound Aerolone Compound is a combination of bronchodilators in propylene glycol solution These bronchodilators are best used with the simple hand bulb nebulizer Occasionally patients employ a solid dust type of aerosol of isopropylarterenol administered by inhalation of the drug in powder form (Norisodrine)

The ease of administration and almost instantaneous relief of bronchospasm obtained in this manner are the assets of this form of therapy These are countered by the obvious liabilities This is only symptomatic treatment and may delay the necessary investigation of the cause of asthma Some patients become psychologically addicted to the nebulizer and do not budge unless they carry the apparatus and medication with them Others abuse the medication by taking it too often and in excess thereby producing states of anxiety along with fastness to the drug

Aminophylline may also be used successfully as a bronchodilating aerosol although it is less efficient than the sympathomimetic amines[3] It cannot however be used with the ordinary hand bulb type of nebulizer With the steam generator and aerosolizer used by the author combinations of aminophylline and Isuprel (1 200) may be employed with excellent results

Antibiotics Next to be introduced in aerosol form were the chemotherapeutic agents and antibiotics Not all of these can be used in this manner for technical reasons—insolubility instability in solution etc—or because of irritative action on the bronchial mucosa Most often this is due to high acidity or excessive alkalinity and adjustments have to be made to counteract this As previously noted propylene glycol when used as a vehicle helps to overcome the irritation although it does not seem to affect the pH of the solution

The antibiotics most commonly administered as aerosols are penicillin streptomycin Terramycin and bacitracin More recently polymyxin and neomycin have been added to the growing list Erythromycin prepared for intravenous therapy has also been used by the author with good effect

For acute infections of the respiratory tract single antibiotics may be employed For chronic infections it is best to investigate bac

teriologically and to employ antibiotics selected on the basis of inhibition testing This may be obviated however by the use of antibiotics in combination A favorite combination of the author contains neomycin polymyxin and bacitracin This combination has the advantage of utilizing antibiotics not ordinarily encountered by the patient which avoids the problem of resistance Furthermore these antibiotics are best administered as aerosols for respiratory infections To this combination may be added penicillin streptomycin or Terramycin Where prolonged treatment is indicated frequent changes in the combinations of antibiotics may help to avoid the development of bacterial resistance

Aerosols of antibiotics may also be used prophylactically in those cases where asthma follows respiratory infections The local topical application of these antibiotics during the viral phase of the common cold may prevent the secondary bacterial phase from developing *accompanied by asthma Both the patient and the antibiotic* should be chosen with care since this prophylactic use can lead to abuse

Mucolytics In recent years mucolytic agents of various kinds have been introduced as aerosols in the treatment of asthma and other bronchial conditions associated with thick gelatinous sputum[4] Unlike the bronchodilators and antibiotics which have proved their usefulness and are generally accepted as aerosols the mucolytics are not yet in general use Although some investigators have been enthusiastic over their usefulness their true value remains to be established

The mucolytic agents may be grouped into simple chemicals such as ammonium chloride surface active agents such as Triton A 20 contained in Alevaire and enzymes such as trypsin and Dornase Last but not least is steam a highly effective mucolytic agent

Ammonium chloride was introduced a number of years ago but was never generally accepted Since it was employed with the steam generator it is possible that the major improvement noted was due to the steam

The surface active agents are numerous and must be used with care since some of them are toxic Alevaire is a compound containing sodium bicarbonate glycerin and Triton A 20 This chemical along with other surface active agents and trypsin has been investigated by Wasserman[7] Using the sputum of asthmatic patients and measuring its viscosity and surface tension before and after mixing with these agents it was found that none affected the surface tension and only one trypsin affected the viscosity It is possible that Alevaire when employed as directed introduces sufficient water

along with sodium bicarbonate to produce some degree of mucolysis

Trypsin and Dornase are said to effect mucolysis through enzymatic action Conflicting reports about their usefulness and their irritating action particularly for trypsin prohibit their indiscriminate use

LIMITATIONS AND ABUSE OF AEROSOL THERAPY

Like all modalities aerosol therapy has limits to its use The following are the most frequent abuses encountered

1 Employment of inefficient apparatus The aerosol particles may be too large and settle in the upper air passages or they may be too small and escape on exhalation

2 Materials may be too concentrated resulting in considerable loss unless a closed system is used or causing irritation of the bronchial mucosa

3 Aerosols may be too cold when administered As they expand from the nebulizer they lose heat and when inhaled cold initiate coughing spells

4 Continued use of oxygen or air may dry the mucous membranes These gases should flow through water before reaching the nebulizer

5 Aerosols of antibiotics should be administered with a regularity comparable with that of oral therapy Too often one hears of treatments given once or twice weekly This must be condemned since it can only result in the development of bacterial resistance

6 Finally aerosols of antibiotics should not be given during an attack of asthma lest they aggravate the condition It is better to precede the antibiotics with bronchodilators During bronchospasm the antibiotics cannot be inhaled in sufficient quantities to be utilized effectively

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60 | *Sheppard Siegal and Milton H Adelman*

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ALLERGY AND ANESTHESIA

A major problem of anesthesia in allergy is the management of anesthesia for the patient with bronchial asthma Less common but of significance is the problem of allergic reactions to anesthetic drugs or to medications used in relation to anesthesia most particularly allergy to local anesthetics

THE MANAGEMENT OF ANESTHESIA IN BRONCHIAL ASTHMA

The asthmatic patient may present significant problems to the anesthesiologist because of impairment of pulmonary ventilation and irritability of the bronchial tree Abnormality of ventilatory mechanism may be readily demonstrated by a reduction in either total or timed vital capacity (see Chap 14) There is almost invariably a diminution of maximum breathing capacity Pulmonary ventilation is uneven and there may be impairment of pulmonary mixing A diminished ventilatory response to CO_2 and in some instances decreased oxygen saturation of the blood may be encountered Depending on the degree of advancement of the disease and the particular status of the patient s asthma at the time there may be considerable variation in the extent of these changes In the patient with intractable asthma of long standing particularly when complicated by emphysema there will be greater degrees of impairment and more *significant hazards and difficulties in anesthesia*[1,2]

Elevated arterial CO_2 and anoxemia are dangers of which the anesthesiologist must be constantly aware as they may be aggravated

in the course of anesthesia The induction phase of anesthesia ma be both difficult and prolonged in such patients The administr tion of the anesthetic is further complicated by the bronchial ir ritability which is characteristic of asthma In addition there i proneness to bronchostenosis with patchy or even massive atelecta sis and heightened susceptibility to bronchopulmonary infection For all these reasons the proper preanesthetic preparation of these patients the judicious choice of anesthetic and above all the skill ful handling of its administration as well as meticulous postanes thetic observation and care are of importance in the optimal man agement of anesthesia in the asthmatic patient

Preanesthetic Preparation Elective surgery should not be per formed in the presence of active bronchial asthma On the other hand emergency surgery may be undertaken despite intractable even severe bronchial asthma Before anesthesia and surgery every needed measure should be instituted to bring the asthma under con trol as completely as possible The aim is to achieve maximum im provement in pulmonary function in advance of anticipated surgery All accepted antiasthmatic medications including steroids and ACTH may be used unless there are medical or surgical contra indications to the latter agents The antihistamines while of little use in adult asthma may be helpful in children

In asthma of severe degree intravenous hydrocortisone may be given before and during the procedure This measure may be of particular importance in patients who have recently had steroid therapy and who therefore require additional steroid to sustain the adrenals under the stress of surgery and anesthesia Antibiotics should be employed whenever there is evidence of complicating in fection especially if steroids are being used The choice of the anti biotic agent will be governed not only by the requirements of the infection but also by evidence of allergy to any of these agents par ticularly to penicillin which should be carefully evaluated

Preoperative agitation should be minimized to avoid precipita tion of an asthmatic attack during anesthesia Repeated reassurance by both the patient s physician and the anesthesiologist is of the ut most importance in allaying anxiety Short acting barbiturates such as pentobarbital or secobarbital are helpful and distinctly prefer able to narcotics either morphine or meperidine (Demerol) as pre anesthetic medication The barbiturates seldom depress respiration do not cause nausea and vomiting and unlike the narcotics do not release histamine and therefore are unlikely to induce broncho spasm [3, 4] Before operation inquiry should be made as to allergy to drugs particularly the barbiturates anesthetics and antibiotics

Atropine and scopolamine while usually employed to reduce respiratory secretions and to inhibit cholinergic reflexes may in the patient with severe asthma have the disadvantage of aggravating the tendency to formation of inspissated obstructive bronchial mucus which is a significant danger to such patients The use of these agents may therefore be contraindicated

For extreme preoperative apprehension such as may occur in children the administration of the basal rectal anesthetic tribromo ethanol in amylene hydrate (Avertin) in doses of 70 to 80 mg per kilogram of body weight may be of great usefulness This agent possesses bronchodilator action and its chief disadvantage its action as a respiratory depressant can be minimized by limitation of its administration to these dosage levels

General Anesthesia The intravenous thiobarbiturates such as thiopental (Pentothal) and thioamytal (Surital) are contraindicated in bronchial asthma as they may initiate bronchospasm

Of the inhalation anesthetics cyclopropane must be used with caution as it tends to induce bronchoconstriction Nitrous oxide and ethylene are both relatively weak anesthetics but may be used in induction preliminary to ether anesthesia Diethyl ether is by far the most versatile and most useful of all inhalation anesthetics for the asthmatic patient It is not only potent but also possesses a bronchodilator effect of sufficient degree so that in the past it has been applied as a therapeutic measure in the control of otherwise intractable asthma It is therefore the inhalation anesthetic of choice for the patient with bronchial asthma

Spinal and Regional Anesthesia Spinal anesthesia is satisfactory in bronchial asthma only for operations which can be performed with an anesthetic level below the tenth thoracic dermatome—so-called low spinal anesthesia In this group are included operations on the lower extremities perineum urinary bladder and inguinal area as well as vaginal deliveries At this level spinal anesthesia does not further compromise the impaired pulmonary function of the asthmatic patient as would higher levels of anesthesia which interfere with the action of the respiratory muscles Regional anesthesia also has its place for the asthmatic patient It must be stressed however that before consideration can be given to the use of a spinal or regional anesthetic in an asthmatic or allergic patient a careful history must be taken to exclude the possibility of a hazardous reaction to the anesthetic agent The problem of allergy to local anesthetics is discussed at length below If doubt persists as to a possible adverse reaction it is preferable to resort to general ether anesthesia Some advise avoidance of spinal anesthesia in the asthmatic

patient because of the factor of anxiety in operations on a conscious patient However with the use of appropriate precautions to manage apprehension experience with low spinal anesthesia in the presence of bronchial asthma has been most favorable

Muscle Relaxants These agents are now so widely used in anesthesia that their application to the asthmatic patient deserves discussion Certain muscle relaxants release histamine and are therefore unsuitable for such patients Among these may be mentioned *d* tubocurarine dimethyl tubocurarine benzoquinonium and gallamine in descending order of potency as histamine liberators In contrast decamethonium suxethonium and succinylcholine do not in ordinary dosage release histamine[5] The last named is the muscle relaxant of choice in asthma for it is short acting and can be controlled continuously as a dilute intravenous infusion Some observers have reported this drug as actually useful in overcoming bronchoconstriction It should be mentioned that the antagonists to the excessive effects of the relaxants are all parasympathomimetic drugs which also induce asthma and must therefore be avoided

Acute Bronchial Asthma during Anesthesia Bronchospasm is not rare during general anesthesia and is not limited to the allergic or asthmatic patient Precipitating causes include aspiration of blood or tracheal secretions visceral traction under light anesthesia and the probable release of histamine or other tissue substances owing to the trauma of operation

The asthmatic attack during general anesthesia is best handled by the introduction of diethyl ether into the breathing circuit of the anesthesia apparatus or by deepening an already existing ether anesthesia Deep anesthesia is required to relax bronchoconstriction but care must be taken to avoid circulatory or respiratory depression Isopropylarterenol (Isuprel) may be employed by nebulization into the breathing circuit or by parenteral administration Epinephrine is avoided during inhalation anesthesia because of the risk of precipitating ventricular fibrillation especially in the presence of cyclopropane

Postanesthetic Care When there is evidence of excessive retained secretions or undue respiratory embarrassment in the asthmatic patient the anesthesiologist may order immediate postoperative bronchoscopy with aspiration of tracheobronchial secretions This may also be indicated if auscultation of the patient reveals evidence of atelectasis In the later postoperative period the asthmatic patient must be carefully watched for the development of pneumonia or other respiratory infection

ALLERGY TO ANESTHETICS

Allergic reactions to the agents used in local regional and spinal anesthesia are well documented although fortunately they are uncommon. In contrast, inhalation anesthetics are scarcely ever incriminated as allergens. In its hundred year history ether has been recorded as causing an allergic reaction but once. Cyanosis and collapse with subsequent pruritus and edema of eyelids and extremities occurred. Simple contact of the skin with ether induced a huge urticarial wheal. This positive test could be confirmed by the passive transfer reaction indicating its immunologic character.[6]

Drugs used as preanesthetic medication, especially the barbiturates, may induce allergic eruptions with or without fever. Pentobarbital may also elicit an unusual bullous reaction affecting the lips, mouth, tongue and genitals. Nonetheless the most common allergic reactions of the postoperative period are those due to the antibiotics, particularly penicillin.

Local anesthetics have long been a source of concern as a cause of anaphylactic shock and sudden death. While some of the reactions characterized by excitement and convulsions are due to overdosage and too rapid absorption from vascular areas, others appear to be truly anaphylactic in character. Procaine, in many ways the safest of local anesthetic agents, has been the cause of anaphylaxis in several well documented reports.[7, 8] Pontocaine administered by injection or topically to membrane surfaces has been more frequently incriminated in fatal episodes.[9, 10] Allergic shock, asthma and rhinitis have been induced by cocaine in exceptional instances.[11] Skin tests with the local anesthetics have proved valueless for the avoidance of these acute allergic reactions.

More recently procaine has been reported as a cause of local allergic edema at the site of injection.[1, 14] The swelling appears several hours after injection and may last a few days or as long as two weeks. Local pain or itching may be present. There is no evidence of accompanying generalized cutaneous or systemic reaction. In such cases a specifically diagnostic positive skin reaction of the tuberculin twenty-four-hour type may be elicited. In three instances[14] there was cross sensitization to Monocaine, an anesthetic with a chemical structure little different from procaine (Fig. 60-1).

Experience with contact dermatitis due to procaine indicates that members of the procaine group, all para-aminobenzoic acid esters, are most likely to show such cross reactivity.[15] In the presence of allergy to any one of them it is preferable to seek safety with anesthetics of a distinctly different chemical configuration. Nupercaine

has been substituted in the past and currently Xylocaine appears to be the most available effective and safe substitute

Local allergic edema due to injected procaine has attracted attention particularly in recent years although this agent has been in widespread use for almost half a century The occurrence of positive twenty four hour skin tests to penicillin in two of three such cases together with the finding of positive procaine reactions in two patients with penicillin allergy suggests that the almost universal use



Fig 60 1 Positive 24 hour skin test reactions to procaine and monocaine in a case of local allergic edema caused by procaine.

of procaine penicillin may be a source of origin of this type of procaine hyperreactivity[14] These observations may call for increased awareness of a possible hazard attendant upon the use of this anesthetic in spinal anesthesia

Careful questioning of patients before administration of a local anesthetic and especially before spinal anesthesia is a necessary precaution A history of a previous reaction to a local anesthetic is of obvious significance but a general history of allergy and especially of reactions to drugs or serum should put the anesthesiologist on guard Unfortunately preliminary skin tests are generally of n-

value Only the twenty four hour procaine skin test probably has value in predicting a reaction of local allergic edema For this reason where the history is doubtful it may be an additional desirable precaution to administer a preliminary trial dose either subcutaneously or as drops into the lower anterior lip fold If no reaction occurs in fifteen minutes the hazard of an anaphylactic reaction is minimized

Allergic contact dermatitis to local anesthetics is a well established entity Among dentists procaine dermatitis of the fingers is an occupational disease [16] just as Pontocaine dermatitis may be among ophthalmologists Occasional instances of contact allergy have been reported among patients using eyedrops of nupercaine [17] larocaine [18] or Pontocaine [19] Benzocaine is a common sensitizer as a topical anesthetic application to the skin In all these instances patch tests are diagnostic

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TREATMENT OF EMERGENCIES IN ALLERGY

The commonest emergencies encountered in allergy are intractable asthma severe serum sickness acute angioneurotic edema in the vicinity of the glottis and allergic shock Most of these emergent states can be reproduced by unwittingly surpassing a patient s tolerance during tests or treatment Each depends on an antigen antibody reaction of the so called early or immediate variety clinical manifestations varying with the intensity and the location of the reaction Restoration of normal function calls for the adroit application of physiologic [1, 2] and pharmacologic principles [3]

STATUS ASTHMATICUS

When the edematous mucus laden spasmodically contracted bronchioles of an asthmatic individual fail to respond to therapy for days the patient is said to be in *status asthmaticus* His clinical appearance will vary with the intensity of his alveolar underventilation and the degree to which he is hyperventilating in an effort to overcome faulty gas exchange It also will be modified by such complications as respiratory infection chronic emphysema cardiac failure and misguided therapy with narcotics oxygen or epinephrine

The fundamental difficulty in asthma is impairment of the gas exchange which takes place between the air in the alveoli and the blood in the surrounding capillaries The oxygen exchange is the

first to become abnormal the carbon dioxide exchange being disturbed only in more advanced alveolar hypoventilation This is because the dissociation curve of carbon dioxide in the blood is such that excessive amounts of this gas can be released into those alveoli which are well ventilated thereby compensating for the limited transfer in poorly aerated alveoli The dissociation curve of oxygen precludes this compensatory opportunity Soon after hypoventilation of the alveoli takes place therefore hypoxemia develops The lowered oxygen tension soon threatens injury to the central nervous system and other tissues Mental disturbances may take the form of exhilaration fixed ideas delirium or mania The condition will be exacerbated if the respiratory center is depressed by narcotics or anesthetics Indeed when hypoxemia becomes severe drowsiness coma and death may result It is paradoxic that high concentrations of oxygen may halt respiration in subjects with marked hypoxia and carbon dioxide retention This occurs because breathing is now being governed by the influence of anoxia on the peripheral chemoreceptors of the carotid and aortic bodies and the stimulus is suddenly removed by the heightened oxygen content

Complications There may be several complications *Dehydration* may develop from the patient s neglect of his fluid and food intake as well as from exertional hidrosis Severe water and salt deficiency may lead to oliguria increased hematocrit alterations in plasma chemistry psychotic manifestations and even circulatory failure Overmedication is common When epinephrine is given parenterally in excessive amounts it can produce systolic hypertension tachycardia extrasystoles and ventricular fibrillation[3] Opiates and barbiturates depress the breathing center as well as the cough reflex and hamper the action of the bronchial cilia which aid in the evacuation of mucus (see Chap 26) *Emotional disturbances* are not only engendered by severe dyspnea but may themselves trigger and maintain bronchospasm (see Chaps 8 and 9) *Respiratory infection* is a frequent and important complication It may either provide allergens which initiate bronchospasm or it may increase the difficulties in a *preexistent asthma by inciting inflammatory edema and mucus secretion* in the airways Furthermore the associated fever and coughing enhance the metabolic need for oxygen and the accumulation of carbon dioxide thereby increasing the burden of the respiratory organs (see Chaps 20 and 52) *Cor pulmonale* with failure of the right ventricle is a primary complication of bronchial asthma and emphysema Alterations in the pulmonary bed raise the vascular resistance thus bringing about pulmonary artery hypertension If the resistance is great enough the right ventricle fails Asthma and

emphysema are the important causes of this type of myocardial failure of the high output variety[4]

Emphysema is commonly associated with long standing asthma It may as a matter of fact be the result of repeated bouts of broncho spasm Indeed there is growing accord among pulmonary phys iologists that the fundamental defect in emphysema is chronic ob struction of the small intrapulmonary airways (see also Chap 24) Whereas the obstruction may be at least partially reversible in the early stages later there is a destruction of the alveolar septa with con sequent loss of support of the bronchioles The latter now tend to collapse during expiration thereby markedly raising the alveolar and intrapleural pressures and encouraging the collapse of more bronchioles[5] Maximal breathing capacity becomes progressively im paired (see also Chap 14) Because of the faulty mixing of gases in the airways and the reduction of absorbing surface in the coalesced alveoli the exchange of oxygen and later of carbon dioxide becomes depressed This leads to various grades of anoxemia and hypercapnia (carbon dioxide retention) which tend to persist and which may be acutely exacerbated by pulmonary infection asthmatic episodes cardiac failure or oversedation Although the effects of hypoxia are exerted predominantly on the vascular and central nervous systems (augmenting the heart rate and causing loss of fluids through the damaged capillaries for example while inciting the mental disturb ances mentioned above)[1] eventually the functions of the kidney heart muscle and many other organs are also jeopardized Hyper capnia leads to muscular weakness headache lassitude confusion ir ritability and personality changes As the carbon dioxide tension mounts the respiratory center not only loses its exquisite sensi tivity for carbon dioxide but the all important cough reflex fails The narcotic effect of high concentrations of carbon dioxide may finally cause coma and death[4] Periodic assays of the plasma carbon dioxide-combining power during an episode of acute pulmonary in sufficiency will serve to indicate the effectiveness of measures taken to improve alveolar ventilation

Management of the Acute Paroxysm

Although such emergencies as acute respiratory or cardiac failure call for immediate attention in most instances of status asthmaticus there is time to procure information from the history physical ex amination and laboratory findings Often this will reveal the cause of the current paroxysm the extent of departure from normal respira tory and cardiac function and the major complications An early electrocardiogram roentgenogram and venous pressure determina

tion will sometimes clarify a presumptive diagnosis An elevated carbon dioxide–combining power carries the implication that carbon dioxide has been retained for at least some hours permitting the slow homeostatic process of bicarbonate retention to be initiated by the renal tubules

If the attack was clearly induced by some inhaled ingested or injected allergen contact should be interrupted at once Luckily a hospital room is usually lacking in significant amounts of common inhalant allergens especially if there is no comforter on the bed the floors are wet mopped and the pillows and mattress contain only foam rubber or horsehair An air filter will remove any pollens that might be contributory while a colonic flush followed by dietary restrictions should halt the supply of ingestible excitants Cessation of therapy with an allergenic antibiotic drug or foreign serum may not bring relief for some days owing to the slow elimination of such agents Allergens engendered by invading bacteria are best obviated by chemotherapy

Aside from these efforts to interrupt an antigen antibody reaction the major emergency steps will be biochemically oriented aimed at the restoration of normal gas exchange and of homeostatic balance in fluids and electrolytes Stubborn bronchospasm especially in the epinephrine fast patient may yield only after cortical steroids have been added to the primary efforts to improve ventilation (see Chaps 26 and 57)

Restoring patency to the airways is of paramount importance The sympathomimetic amines usually afford prompt relaxation of constricted bronchi especially if administered in full dosage and in an aerosolized state Because the effect of those agents is essentially limited to the bronchi adrenergic aerosols have frequently replaced the parenteral use of epinephrine in asthma even when the volume to be placed under the skin or in the muscle is restricted to 0 3 ml of the 1 1 000 preparation In nebulized state ½ to 1 ml of 1 100 epinephrine hydrochloride or of 2 25 per cent Vaponefrin (racemic epinephrine hydrochloride) can be administered for severe paroxysms as often as once an hour[4] For less intense symptoms an interval of two to three hours will be suitable Isuprel 0 5 per cent is also effective but this adrenergic amine tends to cause palpitation tachycardia and arrhythmia by its action on the automaticity of the atrial muscle and the pacemakers[3] As the paroxysm subsides the interval between aerosal treatments can be lengthened the volume being gradually decreased until about one tenth of the emergency requirement is reached When indicated half the volume of the amines may be replaced by 1 per cent Neo-Synephrine a powerful vasoconstricting

agent which will increase the caliber of the bronchial lumen by reducing edema (For a detailed discussion of aerosol therapy see Chap 59)

Occasionally response to the foregoing may prove inadequate particularly if excessive amounts of epinephrine 1 1 000 have been given under the skin In this circumstance aminophylline will be found effective as a bronchodilator[3] If administered by rectum 0 5 to 0 7 Gm along with about 20 ml of water will relax the bronchial smooth muscles in forty five minutes Alternatively aminophylline is available in suppository form The effect of either appears equal to that achieved by intravascular therapy lasting for about two hours If the intravenous route must be used the dose of 0 5 Gm should be introduced during no fewer than eight minutes Serious systemic disturbances result if the xanthine is thrown out of solution during rapid injection owing to the pH of the blood Any leakage into the tissues surrounding the venipuncture will evoke considerable pain Therapy may be prescribed twice daily for four or five days

Oxygen may be needed if the foregoing fail to overcome dyspnea cyanosis and hypoxemia It is mandatory to correct hypoxia promptly if injury to central nervous and other tissues is to be averted Oxygen may be delivered in several ways a hood or large tent being preferable in some circumstances whereas in others intermittent positive pressure breathing especially in inspiration is more effective The latter procedure can be adapted to provide artificial respiration for patients in respiratory failure It also serves to deliver aerosols to the small intrapulmonary airways when an asthmatic patient is unable to inhale deeply because of weakness Principles underlying the use and care of inhalational apparatus have been set up by the Committee on Public Health Relations of the New York Academy of Medicine[7]

Evacuation of accumulated secretions from the airways will not only reduce local irritation which predisposes to cough spasm and dyspnea but also will often improve ventilation strikingly Therefore if inhalational therapy with adrenergic bronchodilators does not produce adequate expectoration a mucolytic detergent such as Alevaire or a proteolytic enzyme such as pancreatic Dornase may be tried in aerosolized state[8] although some allergists have been disappointed by these agents (see Chap 57) Alevaire 2 to 5 ml of 0 125 per cent and from 50 000 to 100 000 units of Dornase can be delivered during a ten minute nebulization period once to three times daily for not over a week Bronchoscopic aspiration and lavage may be indicated for the patient who has a persistent harsh useless cough and trapped secretions which encourage bronchospasm This pro-

cedure is rarely employed now since the advent and development of the steroids

Tracheotomy should be undertaken if accumulations cannot be evacuated by more conservative means An endotracheal catheter for example will seldom prove effective in withdrawing viscid mucus Although bronchoscopy is more efficient it requires preliminary anesthesia of the passageway and this results in inhibition of the cough reflex and of ciliary activity It also causes an occasional untoward reaction Furthermore when the problem of blocked secretions recurs at frequent intervals it is not feasible to repeat bronchoscopy Tracheotomy on the other hand allows periodic cleansing of the airways for many days Trauma will be minimal if the postoperative routine of Plum[9] is followed Since the indication for tracheotomy in asthma is more common than is generally supposed both the allergist and the general practitioner should be able to perform the emergency as well as the elective procedures[10] On the other hand when the physician feels impelled to await the arrival of a specialist he may have to insert a 14 or 16 gauge needle into the cricothyroid space to afford a temporary airway for a suffocating patient Once the tracheotomy tube has been inserted it can be used as the means of introducing aerosols oxygen helium-oxygen mixtures and intermittent positive pressure breathing

Digitalization should be rapidly effected if there are signs of heart failure On the first day digitoxin 1 2 mg can be given at once or 1 4 mg in several divided doses Thereafter 0 1 or 0 2 mg daily serves as maintenance therapy Salt restriction as well as a diuretic for one or two days also may be required

Infection may be the cause of an attack The predominant organism of an acute sinusitis bronchitis or pneumonia should be determined by means of a culture[11] A broad spectrum antibiotic such as tetracycline can be given immediately after the specimen has been procured If 500 mg of tetracycline three times daily does not provide improvement within one or two days especially when the culture reveals staphylococci or Friedlaendler bacilli a series of sen*sitivity tests should be set up with the predominant organism* Penicillin tetracycline chloramphenicol streptomycin erythromycin and novobiocin should be tested Subsequent management is then guided by the outcome (see also Chaps 20 21 52)

Corticotropin and adrenocortical steroids exert a dramatic effect on all expressions of allergy including acute asthma[1] Corticotropin which must be administered by needle will be suitable for those non Addisonian individuals who cannot take oral medication and who can safely wait several hours for maximal hormonal effect From 20 to

25 U S P units of lyophilized ACTH is infused in isotonic saline or in 5 per cent dextrose solution 2½ to 3 liters being delivered during eight to twenty four hours Although this may be repeated for several days oral medication with adrenal corticosteroids should be substituted as early as possible Alternatively an intramuscular injection of 10 to 80 clinical units of ACTH gel is given daily the amount being gradually reduced to 10 or 20 units Fifteen to eighteen hours will elapse before maximal effects are noted Further discussion of steroid therapy asthma can be found in Chap 57

Cortisone and hydrocortisone are preferably given by mouth The acetate suspensions are unsuitable for emergencies since they cannot be injected into the bloodstream and their release from the muscle is much too slow On the other hand the free alcohols may be delivered into a comatose patient by slow infusion during eight or more hours no fewer than 500 ml of isotonic saline or of 5 per cent dextrose solution being used for the 100 mg dose of either steroid Relief may begin in fifteen to thirty minutes and persist for an hour or two after the drip is discontinued Although continuous therapy at the maximal utilization rate of 12½ mg an hour has been carried on for many hours it is usually possible and always preferable to use oral tablets after one or two infusions Severe bronchial asthma as well as hypotensive reactions to drugs have responded well to intravascular management Hyrdocortisone sodium hemisuccinate can be similarly administered as an infusion Indeed in an extreme emergency the 100 mg dose can be dissolved in 2 ml of water and injected at once Although therapy with this soluble hydrocortisone (Solu Cortef) can be continued with doses of 50 mg at intervals of one three six and ten hours in prolonged crises it is conservative to give cortisone or hydrocortisone acetate intramuscularly at the time of the initial intravascular injection Fifty milligrams of either microcrystalline suspension will provide peak activity in eight to twelve hours while less striking effects may be noted as early as three hours and as late as twenty four Only a moderate metabolic result should be expected of these suspensions which are intended primarily for intra articular use but which may facilitate the discontinuance of intravenous therapy If prolonged parenteral therapy is indicated especially when intravascular treatment is also being continued intramuscular injection of the 50 mg dose can be repeated at six hour intervals during the first day at eight hour intervals on the second and third days and at twelve hour intervals on the fourth and fifth days It will almost always have proved feasible however to institute oral therapy during this period

Prednisone (Meticorten) and prednisolone (Meticortelone) are re

cent modifications of the natural steroid cortisone They appear superior to their precursors in antiallergic qualities and have so little influence on the salt and fluid balances that sodium restriction and potassium supplements are commonly omitted [13] (see Chap 57)

Fluid and sodium deficiencies are best corrected by mouth especially if there is any question of cardiac insufficiency

Acute morphine poisoning can be countered by 5 to 10 mg of nalorphine (Nalline) by vein [3] If respiration is not adequate in ten or fifteen minutes the dose may be repeated until the total is brought to 40 mg Additional therapy may be required every three or four hours Although Nalline is ineffective in respiratory depression caused by barbiturates or ether it is useful against morphine derivatives and synthetic narcotics

Iodides may be indicated during the acute phase of asthma if the mucus is viscid and the cough is dry Although some allergists recommend 0 5 to 1 Gm of the Sodium salt intravascularly once daily iodides are too irritating to be suitable for acute inflammatory conditions of the airways and are best reserved for the later stages of bronchitis Iodides are frequently allergenic and are specifically contraindicated in tuberculosis Consequently it is more conservative to select sodium or ammonium chloride for purposes of liquefaction It is important that a large tumblerful of water be prescribed with the 0 3 to 0 5 Gm dose of these chlorides which can be repeated every hour or two if needed

Insomnia can usually be overcome with 0 5 to 1 Gm of chloral hydrate or with 3 to 15 ml of the equally unpalatable paraldehyde They should be flavored with orange syrup and diluted abundantly in water when offered by mouth Alternatively chloral hydrate can be given in olive oil or in suppository form by rectum while paraldehyde is often administered as a small retention enema Ether in-oil by rectum has also been used to relieve emotional tension and bronchospasm

Ephedrine is reserved for the period of convalescence and for mild asthma (see Chap 26)

SERUM SICKNESS DRUG ALLERGY AND ANALOGOUS DISORDERS

At the outset it is more urgent than in status asthmaticus that contact with the offending allergen be promptly broken As early as possible therefore a detailed history must be procured with reference to fever eruption or other untoward responses that follow an incubation period Steps can then be taken to separate patient from

excitant if there is a current exposure Repeated episodes of increasing severity and progressive dispatch are especially revealing In tracutaneous and ophthalmic tests with a suspected foreign serum insect venom or 40 unit crystalline insulin can start with 0 01 ml of 1 10 000 material tenfold increments being employed at five minute intervals until slightly active concentrations are determined A response to conjunctival instillations will carry much more practical significance than will a wheal and flare reaction induced by an endermal injection Although drugs rarely provide responses of either type it is permissible albeit frequently unrewarding to explore the cutaneous state by introducing minute amounts of likely excitants into the skin through a scratch or an intracutaneous injection Meanwhile much may be gained if the patient is kept under careful surveillance for any systemic manifestations during the next several hours The initial strength of such a drug as penicillin G in crystalline form could safely be 100 units per milliliter followed by 1 000 and finally by 10 000 units per milliliter Alternatively from 10 000 to 50 000 units can be tested orally (see also Chap 47)

Regardless of one s success in uncovering the probable cause of the patient s attack the next step is to gauge and repair the damage Since serum sickness and allied allergies are generalized disorders physical examination is imperative Conventional studies of the blood urine circulatory and other systems should include roentgenograms electrocardiogram and comparable diagnostic procedures Symptomatic therapy can then be guided by the findings

Since capillary dilation and leakage combined at times with smooth muscle constriction comprise the essential derangement [15] in this type of illness the ideal therapeutic agents will be those which quickly correct the basic fault One need look no further than the adrenal gland Its medullary hormones epinephrine and norepinephrine antagonize the effects of histamine on the capillaries bronchial smooth muscles and some of the arterioles while two of its cortical secretions cortisone and hydrocortisone protect allergic tissues against the inflammatory action of antigens The success of the physician will depend largely on his ability to cooperate with nature in aiding the homeostatic responses of this gland Epinephrine 1 1 000 is the traditional remedy about 0 3 ml being placed in the muscle If this is effective ½ to 1 ml of 0 2 per cent epinephrine in oil intramuscularly will provide a more gradual influence which commences in about thirty minutes and persists six to eight hours An aqueous suspension of epinephrine base 1 200 accomplishes the same result when employed in a volume of 0 2 to

0 3 ml under the skin If hypotension complicates serum sickness phenylephrine (Neo Synephrine) is more suitable than epinephrine (see Anaphylactic Shock below)

Antihistamines which block the access of histamine to the receptor sites in the cell are logical agents for serum and drug reactions especially when urticaria and hay fever-like manifestations are present in mild form Among the many varieties Pyribenzamine and Benadryl are commonly effective when prescribed in 50 mg doses at four hour intervals either by mouth or for emergencies by slow infusion The oral dose of Chlor Trimeton is 4 mg whereas 20 mg may be given by slow infusion (see Chap 58)

The *cortical steroids* notably prednisone prednisolone methyl prednisolone triamcinolone and hexamethasone will afford dramatic relief of symptoms If rapid control is sought prednisolone is introduced into the circulation as described earlier If not available hydrocortisone can be substituted ACTH provides a more delayed effect Concurrent chemotherapy may also have to be considered

Codeine Demerol or salicylates may be required as *analgesics* if joint pains are distressing

ACUTE ANGIONEUROTIC EDEMA

Angioedema is essentially urticaria which involves the subcutaneous and submucosal tissue diffusely It may cause alarming obstruction of the airways when it affects the region of the larynx Indeed if intramuscular epinephrine or Neo Synephrine fails to widen the lumen and the corresponding aerosol has likewise been ineffectual tracheotomy[10] must be performed when asphyxia threatens Intravascular therapy with 50 mg prednisolone or with 100 mg hydrocortisone hemisuccinate in a few milliliters of diluent might act rapidly enough to meet the emergency To encourage loss of fluid a diuretic in conjunction with saline purges may be recommended for patients who can swallow Antihistamines repository epinephrine and ephedrine should sustain control once the critical stage has passed (see also Chap 31)

ANAPHYLACTIC SHOCK

Although peripheral vascular collapse can result from any extensive antigen antibody reaction of the immediate variety the commonest offenders are horse serum and chemotherapeutic agents ad

ministered by needle In the author s experience shock has also been induced by insulin wasp venom and overdoses of seed and pollen extracts Only rarely has the gastrointestinal tract served as the portal of entry [16] Nevertheless a mere taste of candy flavored with cotton seed flour led to asthma hay fever abdominal colic and prostra t on within thirty minutes in one woman [1] Ingested penicillin is known to elicit occasional perilous reactions as is also inhaled castor bean dust Although the release of histamine like substance may be so sudden that there is inadequate time for the usual progression of manifestations before collapse and death ensue within a few minutes some of the following signs commonly develop a strange taste (penicillin) widespread flushing urticaria angioneu rotic edema dysphagia crowing inspiration nausea vomiting def ecation hunger pains cold sweats wheezing dyspnea marked pal lor cyanosis visual and auditory disturbances giddiness extreme prostration a sense of substernal constriction and a fear of impend ing death

Frequent measurements of the pulse and blood pressure during ten severe nonfatal reactions to overdoses of therapeutic allergen in my office have revealed changes which were consistent with his tamine release (see Chap 4) The precipitous reduction noted in the diastolic pressure like the generalized erythema and urticaria might have been due to vasodilation The rapid lowering of systolic pres sure to or below the critical level of 50 mm of mercury reflected a probable sharp drop in peripheral resistance which was presumably abetted by a diminution in circulating blood volume poor venous return and reduced systolic output [15] The patients made either a prompt spontaneous recovery on lying down or responded favorably to an intramuscular injection of epinephrine 1 1 000 Bronchospasm was encountered only once

Two factors are held responsible for spontaneous recovery from histamine shock One is the rapid destruction of the amine by the body and the other is the elicitation of compensatory reflexes by sympathoadrenal discharge [15] Although epinephrine released from the adrenal gland will antagonize the action of histamine on the bronchus epinephrine cannot be considered an antagonist of his tamine in the cardiovascular system Indeed its vasoconstrictive effect on the vessels in the skin is more than counterbalanced by its vasodilative influence in the muscles and elsewhere In so far as the net result is a lowering of peripheral resistance epinephrine is synergis tic with histamine accelerating an already rapid heart On the other hand sympathetic nerve activity may be counted on to restore the

systolic pressure by its constrictor action The cardiovascular state observed at any stage of an anaphylactic episode will therefore depend on the balance struck between these conflicting forces

Management

Place the patient at once in the head low Trendelenburg position to overcome cerebral ischemia Although conventional handling calls for the intramuscular injection of epinephrine 1 1 000 in a volume not to exceed 0 3 ml it is wise to instruct an assistant to fill a drip bulb infusion set with a liter of 5 per cent dextrose solution The vessels may be so collapsed that an intravenous catheter has to be employed or a small incision made over the vein If profound vascular collapse persists for more than ten minutes after epinephrine therapy norepinephrine (levarterenol or Levophed) 4 ml can be added to the infusion reservoir to provide a 0 2 per cent solution containing *0 1 per cent of the base The blood pressure response* to an initial injection of 2 or 3 ml is then observed the flow rate being adjusted to establish and maintain the desired level The range is from 80 to 100 mm of mercury for the systolic pressure in previously normotensive patients a little higher in hypertensive individuals The average drip required to maintain normotension is 0 5 to 1 ml per minute (2 to 4 μg of base) Treatment of this sort has been continued without interruption for as long as twenty-one days in shock from hemorrhage trauma or bacteremia Levarterenol can be administered in high concentrations if fluids are contraindicated The 4 ml ampule of Levophed can for example be diluted in as little as 250 ml of dextrose solution In terminating treatment the rate of infusion should be reduced gradually the time devoted to withdrawal being gauged by the patient s capacity to sustain his own blood pressure

If by chance this powerful vasoconstrictor should leak out around the venipuncture infiltrate the area liberally with 5 to 10 mg of Regitine an adrenergic blocking agent admixed with 150 turbidity units of hyaluronidase The infusion needle should meanwhile be inserted into another vein

Phenylephrine (Neo-Synephrine) also has a purely vasoconstrictive though moderate influence on peripheral vessels and hence can be used if epinephrine and levarterenol are unavailable When employed intravascularly in the dose of 0 5 mg, its prompt influence is evident for twenty minutes If placed under the skin or in the muscle *its effect lasts for nearly an hour During recovery from shock* it can be taken orally in an amount ranging from 20 to 50 mg Neo-Synephrine characteristically elevates and sustains blood pressure

with minimal effect on the myocardium and central nervous system As mentioned under Asthma its bronchospasmolytic action is only moderate

Intravascular treatment with prednisolone or with hydrocortisone also has been effective in allergic shock as previously stated Anti histamines are useful in the less severe stages

In general allergic shock requires rapid rather than prolonged attention The homeostatic mechanisms of the body appear capable of asserting themselves once an overwhelming histamine like in toxication has been briefly countered with suitable adrenergic or hormonal antagonists

ADVERSE REACTIONS TO ADMINISTERED ALLERGENS

Untoward responses to allergenic solutions may occur in conjunc tion with either therapeutic or diagnostic procedures in the physi cian s office They result when the amount of antigen applied to a scratch or introduced more deeply with a needle oversteps the patient s tolerance Obviously the accidental or intentional intro duction of allergen into the circulation would increase the risk of adverse systemic effects caused by its rapid dissemination When an allergen reagin combination takes place simultaneously in a large area the release of H substance may be sufficient to cause death

Management In view of the rapid development of the classical wheal and flare reaction which typifies all the untoward responses of the atopic individual it is obvious that both the physician s staff and the patient should be familiar with the premonitory signs and symptoms such as flushing of the face and palms a sense of general body warmth or hives and pruritus remote from the site of the in jection If the administered allergen markedly exceeds the tolerance hay fever asthma hypotensive weakness nausea and collapse may quickly ensue A tourniquet is the first therapeutic need It should be placed above the area of the injection with sufficient firmness to occlude the venous return without obliterating the radial pulse If manifestations commence a few minutes after the patient s con tact with allergen the outcome will usually be more serious than if fifteen to twenty minutes elapse Therefore with a very rapid onset it is often of paramount importance to place the victim in the head low Trendelenburg position on a couch and to treat him for acute hypotension as suggested under Shock If on the other hand the untoward symptoms are mild and delayed in onset either no treatment or an antihistamine by mouth is appropriate If asthma or angioedema develop management can follow the courses outl---

under those headings When release of the immunizing antigen is slowed by its prior emulsification in mineral oil such overdose manifestations as may develop tend to be postponed It is wise therefore to keep the patient under surveillance for an hour after such therapy Furthermore remedial management usually has to be more sustained than when conventional nonemulsified allergen is involved Epinephrine for example is administered not only in the usual fast acting form (intramuscularly) but as soon as its salutory effect becomes apparent the slower acting base is injected as well either as a suspension in vegetable oil for intramuscular use or as an aqueous suspension (Sus Phrene) under the skin This usually provides about six hours of control Antihistamines ephedrine prednisone and related steroids and other agents can be used simultaneously by mouth for added symptomatic control if needed

PREVENTION OF FUTURE EMERGENCIES

After the allergens responsible for the patient s asthma or other allergic episode have been tentatively located by extensive interviews and when the use of antiallergic agents can safely be interrupted cautious testing with likely allergens should be instituted Not only the skin and conjunctiva [16, 17] but in cases of asthma the bronchial mucosa should also be examined The purpose is to strengthen or weaken a clinical diagnosis derived from cause and effect data that have been procured from the history or from deliberate exposures planned by the physician Asthmatic subjects should be examined with a maximal breathing-capacity or a timed vital-capacity test before and after the inhalation of a bronchodilating agent [4] Later the test should be repeated in conjunction with the inhalation of aerosolized allergen If inhalation apparatus is lacking auscultatory evidence of induced bronchospasm will serve as the diagnostic criterion For most drug allergies the only reliable diagnostic procedure will be a clinical provocative test Obviously the amount of drug employed should be minimal and the patient should be kept under continuous professional observation for some days after the experiment Otherwise the hazards will outbalance the advantages of an unequivocal diagnosis

The allergen discovered one can not only speed a patient s recovery but prevent future attacks by the simple device of separating victim from allergen If adequate avoidance is impracticable one can induce a tolerance for inhalant antigens by injecting graduated parenteral doses of the offender This can almost invariable be accomplished for a period of months by administering seven weekly

or semiweekly injections under or into the skin [19] (See Chap 56) Alternatively only one or two annual visits to the office are required if the allergen is emulsified in petrolatum according to the Freund principle and placed under the skin for slow release [0] Either procedure raises clinical resistance by provoking the formation of competitive wheal inhibiting antibodies The antigen is preferentially bound and inactivated by this thermostable antibody which thereby forestalls the antigen s union with the allergic antibody and prevents the allergic response [1] The same mechanism operates when immunization is carried out with venom or insulin

That allergy and immunity depend on two different antibodies is evident from the fact that the sensitizing and blocking activities of the treated patient s serum are separable by electrophoresis convention Furthermore ACTH appears to prevent the formation of blocking factors by man whereas it exerts no influence on the output of allergic antibodies [3]

Prophylaxis of the asthmatic individual should include breathing exercises [4] and psychotherapy Furthermore it is of paramount importance that allergic persons be immunized with appropriate toxoids to preclude their need for borrowed antibodies (against tetanus toxin for example) The prophylaxis of intrinsic allergy usually rests on measures that discourage and combat infection For drug allergies the only insurance is rigorous avoidance

The prevention of overdose reactions has two aspects One consists of the avoidance of technical errors during tests and therapy with allergens The other rests on the physician s judgment of the patient s limit of tolerance for such agents Although many pages would be required to cover this subject fully some of the empirical knowledge accumulated in the author s experience and in the literature can be synopsized

Serious reactions have occurred as the result of either mislabeling extracts in the laboratory or misreading labels in the treatment room Furthermore one can unwittingly employ the wrong volume of the right solution To minimize these risks it is the author s practice to insist that two competent workers participate in every stage of preparation dilution labeling and administration of allergens

Although disastrous reactions are usually referable to therapy they may also arise during diagnostic testing A conscientious assistant should therefore vouch for each label on the tray of solutions as the syringes are filled Since the risk of unfavorable response increases directly with the amount of antigen and with the speed of its absorption the safety of a given test dose diminishes with the testing procedure in the following order cutaneous scarification

conjunctival instillation and intracutaneous injection However the safety of the three methods may be equalized by the simple device of adjusting strengths It is therefore not the procedure per se but the physician s misuse of a given procedure which has brought such technics as the intracutaneous test into occasional disrepute Indeed the scratch method despite its vaunted safety has proved lethal on occasion Furthermore its relative innocuousness may be offset by its insensitiveness In one of the author s studies for example this test with pollen granules failed to evoke any response in half the members of a large group who were clearly allergic according to clinical criteria as well as the intracutaneous and the conjunctival tests

From the foregoing it is obvious that the physician should be conversant with all types of tests employing that best suited to his individual patient as judged by cause and effect relationships which he culls from the patient s history If hypersensitiveness promises to be exquisite diagnostic tests should be initiated with high dilutions of the suspected agents applied to scarifications particularly when the allergens are seeds or beans Stronger preparations can be used after 20 minutes if indicated Finally when endermal injections are begun the testing solutions should be employed initially in high dilution and in small volume It is mandatory that they be placed in areas that are amenable to effective tourniquet therapy *Individuals whose eyes participate in the clinical complaint should ultimately be examined by the conjunctival instillation test* since this is not only the safest and most reliable of diagnostic aids but also serves to classify the patient for therapy [19]

Regarding untoward responses during therapy critical developments can usually be avoided if sufficient precaution is taken Initially for example the threshold of allergic reactivity should be gauged by means of a conjunctival test [19] with the actual batch of allergen that is to be employed for treatment In this way the patient can be assigned to a schedule of dosage which has been well tolerated by others of a comparable conjunctival class The schedule *should be modified if any injection leads to focal manifestations or* to a greater than desired local reaction In our experience the latter should persist for about 48 hours if the course of multiple injections is to be completed with dispatch and with minimal risk Reference to other chapters (Chaps 16 and 56) however will reveal that others prefer to devote more time to treatment in an effort to avoid this degree of local response

The criteria of tolerance to *therapeutic* allergen will vary not only with the physician but also with the form in which the antigen

is injected Localized and systemic responses will for example be strikingly reduced if the assigned dose is first emulsified in mineral oil [9] In general the sequence of doses should be adjusted to the individual tolerance of the recipient This tolerance will depend not only on his original degree of sensitization or reagin output but also on his capacity to produce blocking antibody during therapy [1] Both factors are subject to individual variation and no set sequence of therapeutic doses will be ideal for all patients Moreover since tolerance is expressed in terms of allergen it will appear to change as the extract in use deteriorates with age Hence one should always evaluate a freshly prepared extract in the skin or eyes of a series of patients before utilizing it for therapy Without this precaution adverse responses may follow the transfer If on the other hand one maintains his stock solutions in an equal volume of sterile glycerine as recommended by Hampton loss of potency will be negligible and transition can be made more safely

There are other practical precautions against adverse effects during immunization The physician should for example never fail to write *in advance* of loading his syringe the exact strength type volume and resulting dose he intends to employ A competent assistant then checks the accuracy of these figures as well as the wisdom of the plan and vouches for each step of its fulfillment It is of particular importance that the volume type and strength of the extract be verified *while* the needle is still inserted in the vial If additional allergens are to be included in the same injection enough air to create positive pressure should be preliminarily introduced into each of the prospective vials with a sterile syringe This precludes their subsequent contamination with the syringe contents Moreover immediately after the allotted allergen has been drawn up into the syringe from the container the vial should be placed well out of reach to avoid double measurements After the needle has pierced the skin one always retracts gently on the plunger to make certain that a blood vessel has not been entered In view of the remoteness of vessels from the epidermis there is obviously less risk of intravascular injection when the endermal rather than the subcutaneous or the intramuscular route is selected for therapy An additional advantage of intracutaneous treatment is the relatively slow absorption of antigen from the epidermis It should be remembered in selecting therapeutic preparations that concentrated solutions diffuse more rapidly than dilute ones Hence a specified dose can be injected more safely in a large than in a small volume Another precaution should be taken when the prescribed dose is to be mixed with diluent in the syringe The diluent should be measured

first not the allergen If the reverse order is followed the 0 03 cc of extract present in the lumen of the needle will be drawn up with the diluent introducing an error and encouraging an unfavorable response

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PROPHYLAXIS IN ALLERGY

Allergy according to most authorities affects about 10 per cent of the population Naturally any program that will decrease this high incidence is most desirable Furthermore the prevention of recurrences or exacerbations of existing allergic conditions needs consideration It is the purpose of this chapter to analyze the prophylactic measures available to those engaged in the treatment of allergic patients and to indicate those of practical import

A review of the literature and texts on allergy reveals the paucity of information that is available on the subject of prophylaxis Some of the texts completely ignore this subject others devote only limited space to it The most comprehensive coverage of prophylaxis is to be found in the texts of Walzer *et al*[1] Unger and Glaser[4]

The available knowledge of the mechanisms of allergy is limited and therefore controversial For the purposes of simplification we consider allergy as being caused by an antigen antibody reaction with a release of histamine which affects various shock organs that are in an already *receptive* stage The isolated fact that one has reaginic antibodies in his blood or fixed in his skin or mucous membrane is not sufficient to produce symptoms when contact is made with the specific antigen There are many people who give positive skin reactions or even have skin sensitizing antibodies in their blood as demonstrated by indirect skin tests (passive transfer method) but who are nevertheless free of symptoms There are many factors which make shock organs receptive or excitable Some of these are

massive exposure to allergens infections endocrine disturbances shock and psychogenic disturbances The control of each of these factors may serve as a separate avenue through which prophylaxis may be approached

Another important predisposing factor deserving special consideration in clinical allergy is heredity Statistically Spain and Cooke[4] have demonstrated that where there is a bilateral family history of allergy *the onset of allergic disease is much earlier and more frequent* as compared with those with a unilateral or negative family history of allergy Ratner and Silberman[5] and others do not accept this view Ratner and his coworkers[6] have written considerably on this subject Their conclusions are based on experiments with guinea pigs Female pigs were sensitized with either egg white or horse serum and then were mated with normal males Sensitivity was transmitted passively through the placenta to the offspring and in a certain percentage of cases to the third generation Ratner[7] also presented 15 cases of food allergy in children in which the mother consumed unusually large amounts of certain foods in the antepartum period Sometime after birth the offspring showed sensitivity to these foods On the basis of these findings the experimental evidence of intrauterine sensitization in the guinea pig and the similarity between the placenta in man and that in the guinea pig (in that a single cell layer separates the fetal from the maternal circulation) Ratner concluded that sensitivity in the human being could similarly be induced in utero either actively or passively

While we know that human antibodies such as antitoxins are transmitted through the placenta to the fetus the transference of reagins has as yet not been demonstrated Bell and Eriksson[8] studied ten pregnant women of whom five were sensitive to pollen and five to inhalants and foods In all these cases reagins for these substances were demonstrated in the maternal blood Studies of the serum obtained from the fetal cord at term failed to reveal any of the skin sensitizing antibodies which were present in the maternal blood Walzer[9] and Caulfield[10] confirmed the findings of Bell and Eriksson[8] Zohn[11] induced sensitivity in 12 pregnant women with extracts of *Ascaris* These women were originally negative to *Ascaris* on direct skin tests and by blood studies for reagins After a number of weekly intradermal injections of *Ascaris* the skin reactions became positive At term reagins for *Ascaris* could be demonstrated in 9 of 11 specimens of maternal blood but in none of 11 specimens of fetal blood Until we are able to demonstrate definitely the passage of reagins from the mother to the offspring through the placenta we cannot accept intrauterine sensitization as the mechanism

of production of allergy in the newborn and so we must revert to the concept that allergy is primarily a hereditary disease

In a consideration of the prophylaxis of allergy through the ave nue of heredity eugenic marriages theoretically have merit but they are impractical However parents who are allergic can be educated and advised to take precautions with their children and institute measures early in life in order to prevent clinically significant al lergy Prime consideration should be given to the early recognition of allergic signs and symptoms

What are some of these early signs? We can suspect allergy if any of the following conditions exist

Need for frequent changing of feeding formulas
Persistent sniffles
Unusual and persistent colic
Unexplained diarrhea or constipation
Extreme food likes and dislikes
Vague and unexplained abdominal pain especially periumbilical
Excessive vomiting
Unexplained skin rashes
Unusual amount of unexplained fretfulness and irritability
Repeated canker sores

It is important to emphasize that these symptoms are not pathog nomonic of allergy but where organic diseases have been excluded the possibility of allergy should be considered

There are some who feel that prophylaxis may be attempted at even an earlier level than infancy This implies control of the ma ternal diet in the prenatal period There is no uniformity of opinion however on this subject There are some who believe that strongly allergenic foods such as eggs milk nuts and fish should be curtailed considerably during pregnancy Others take a modified position and allow the mother to have all foods but not in excessive amounts Ex perimentally there is no evidence that the newborn infant is af fected by the excessive ingestion of foods by the mother during pregnancy Those cases in which Ratner demonstrated that children were sensitive to the same foods that the mother ate excessively dur ing pregnancy were not seen at birth but rather months or a year or two after birth Sensitization could therefore have taken place dur ing this interval in many other ways

Prophylaxis in relation to the development of sensitivity to foods deserves special attention A number of procedures have been ad vocated for the treatment of foods to render them less antigenic One of these procedures the denaturation of food whether by chemical treatment or by heat must receive prime consideration

because of its simplicity and usefulness Since milk is the earliest and most important food for the infant denatured milk (boiled evaporated or powdered) is valuable prophylactically Milk substitutes such as soybean milk or meat base milk may at times serve the same purpose Glaser[3] studied a group of newborn babies for whom soybean milk was substituted for cows milk His findings were most encouraging from a prophylactic point of view In his experimental group only 8 per cent developed eczema while in the control group the incidence was 30 per cent Suppression of the development of food allergy in infants does not preclude the possibility of subsequently developing allergies On the other hand it is suggested that the prevention of allergy early in life may buttress the child against the development of allergy subsequently This is only true however for some cases In a follow up study Glaser[3] observed that only 15 per cent of the experimental group developed major allergic conditions before the age of ten years as compared with 60 per cent of the control group In a later study he came to the following conclusion

there is approximately a four fold incidence of allergy in potentially allergic children started on cows milk from birth as compared with those started on soybean milk Denaturation of food therefore serves two purposes it reduces the possibility of specific sensitization and it reduces the possible expansion of the allergic base

In general new foods in potentially allergic children should be introduced with caution Some pediatricians overfeed babies and introduce too many foods very early in life Some infants at two months of age are getting a diet that would be more suitable for a one year old One wonders whether this is justifiable It is true that some infants thrive on this regimen but a great many develop gastrointestinal disturbances The development of allergies in some of these children is greatly increased by the introduction of too many foods too soon

Since egg is an important allergen in infancy special attention should be given to its use particularly in infants born to allergic parents It should not be introduced before six months of age and preferably later When eggs are introduced into the infant s diet only the yolk of the hard boiled egg should be given

Other highly allergenic foods such as wheat also deserve consideration Rice and barley cereals should be given in place of wheat The newborn infant does not have amylase which is the carbohydrate enzyme Then why give cereals so early in life? As far as fruit and vegetables are concerned a gradual introduction is advisable Above all only one food should be introduced at a time and the child should be observed for a week or two for adverse reactions be

fore new additions are made Some pediatric allergists recommend the use of synthetic vitamins in place of orange juice This seems to have some merit

Those interested in prophylaxis for allergic patients have already been alerted to the precautions necessary to avoid the development of allergy to foods No such precautions however are usually offered where inhalants or infections are involved

In the prophylaxis of inhalant allergy it is particularly advisable to reduce exposure to potential allergenic dusts Although house dust is distributed generally throughout the household the bed room needs special consideration because of the number of hours spent there and because of contact with potential inhalant allergens The following precautions should be undertaken to render the bed room relatively dust free

1 Old feather pillows should be removed or if they are in good condition they should be covered with dust proof casings The use of foam rubber pillows with dust proof casings is ideal This also applies to the rest of the house

2 Mattresses should be covered with impermeable materials

3 Floors should be either wooden or covered with linoleum so that they can be washed readily

4 Heavy drapes should be eliminated and washable curtains substituted

5 Overstuffed chairs should be removed and leather or plastic covered chairs substituted

6 Stuffed toys should not be kept in the bedroom and toys made of metal wood or plastic should preferably be substituted

In addition to the above dogs and cats should not be kept in the house Insecticides especially those containing pyrethrum should be avoided

Since it is virtually impossible to render any room absolutely free from dust and since contact with dust in one form or another is inevitable hyposensitization with house dust either stock or autogenous is recommended Similarly sensitivity to pollen should be treated by injection either preseasonally or perennially Reliance for relief on antihistamines or steroids is fraught with danger The incidence of chronic coughs persistent nasal symptoms and bronchial asthma is about 30 per cent in untreated cases and negligible in treated ones

The attempt at prophylaxis of infection in allergic patients is more complex and more difficult It is recognized that many cases of bronchial asthma date their onset from infection whether exanthemata pneumonia pertussis influenza or upper respiratory inf

tions Furthermore recurrent asthmatic attacks are commonly associated with or preceded by upper respiratory infections Likewise allergic symptoms often persist despite all antiallergic measures because of an underlying infection For these reasons the prophylaxis of infection is essential

Prigal[1] has contributed much to a better understanding of infection in its relationship to allergy He firmly believes that infection plays a much greater role than is commonly recognized by allergists or the medical profession in general Infection broadens the base of allergy In its presence new sensitizations are apt to emerge This refers not only to the conversion of latent to active sensitization but also to the triggering of completely new sensitivities

One of the neglected problems in treating and preventing sinorespiratory infections in allergic patients is a lack of consideration of the bacteriologic environment This implies a search for possible carriers who may reinfect the patient Some cases of bronchial asthma or sinusitis will show remarkable improvement when attention is paid to contacts within the household some of whom may harbor pathogenic organisms These individuals are usually free of symptoms By treating these contacts problem cases can at times be cleared up according to Prigal[13]

More important however is the large group of children who develop asthma with each upper respiratory infection With proper and adequate use of antibiotics in the early viral phase many attacks of asthma can be aborted since these are usually associated with the second or bacterial phase of the infection Recurrent asthma is one of the few indications for the use of antibiotics in the early phases of the common cold

The question of tonsillectomy as a prophylactic measure in the allergic or potentially allergic child is raised frequently Certainly indiscriminate tonsillectomy should be condemned Given an allergic child who gets repeated respiratory infections the following procedures are advisable

1 A complete allergic work up should be done and proper measures instituted with regard to food and inhalant sensitivities

2 Hyposensitization treatments should be started early

3 Tonsils should never be removed during the pollen season

4 Removal of tonsils should be recommended only if they are cryptic and diseased The presence of enlarged anterior cervical glands which persist is good evidence of diseased tonsils

5 Complete and thorough removal of adenoid tissue is important (see also Chap 51)

Thus far in our discussion of prophylaxis we have stressed meas ures for infants and children *It is in this group that most can be* accomplished Diseases that have persisted for long periods are not however readily amenable to prophylaxis This approach is there fore more difficult in the adult than in the child However many of the prophylactic measures that we recommend for children apply similarly to adults These are early diagnosis and treatment dust precautions and adequate and early *treatment of infections*

Finally brief mention should be made of the incidence of allergic reactions following the use of diagnostic procedures such as urog raphy cholecystography salpingography and drugs in general The use of antihistamines prior to the administration of these dyes may be helpful in some cases Injectable antihistamines when combined with the dyes offer an even greater margin of safety

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MAJOR PROBLEMS AND NEW HORIZONS IN ALLERGY

Now that the reader has been presented with the various aspects of allergy as recounted in the previous chapters (and the vastness of the field encompassed may have surprised him), it is time to turn to allergy of the future. This can only be done after a consideration of the major problems still confronting the allergist, since these will be the objects of future research.

MAJOR PROBLEMS CONFRONTING THE ALLERGIST

Despite the many achievements of the allergist, there are many problems which remain unsolved. Only the most important for which we seek solution are mentioned here, however. These may conveniently be classified under *diagnosis* and *treatment*.

DIAGNOSTIC PROBLEMS

Skin Testing and the Preparation of Allergens. Should the allergist be satisfied with the diagnostic tools at his disposal? Obviously not, since his most useful diagnostic procedure, the various methods of skin testing, has specific limitations. In the first place, the usefulness of the skin test varies with each allergic disease entity. It is most useful in the respiratory diseases, less useful in the skin allergies, and least useful in allergy of the gastrointestinal and central nervous systems. This raises the question: Why the difference?

Why should a test performed in the skin reflect more accurately the goings on in the respiratory tract while the same test performed in the organ actually involved in an allergic process is apt to be uninformative The skin it seems is the allergic bookkeeper of the body recording past present and perhaps future sensitivity The brain is also a bookkeeper but of a different kind—of experiences learning etc The brain like the skin is also ectodermal in origin and yet despite this same origin skin testing for brain allergy is relatively unrewarding

Consider for a moment the crude methods employed in extracting allergens particularly foods [1] The procedures involved are designed primarily for antigens soluble in aqueous solutions Are all antigens soluble in this medium? Perhaps some antigens are lost by the limited methods of extraction Shall we ignore the fat soluble antigens? It is apparent that the whole problem of diagnostic allergens—their extraction preservation and standardization—needs to be reinvestigated With such new tools as gel diffusion and chromatography (described in Chap 15) various antigenic components can now be identified and perhaps ultimately purified and prepared for testing

Skin testing with viral and bacterial antigens has so far proved of little value in diagnosing viral and bacterial allergy True here we are not likely to have circulating antibodies and yet the simplicity of skin testing is such that efforts must be made to improve their usefulness in detecting allergy from infection

The same problem confronts us in skin testing for drug sensitivity What a boon to allergy it would be if a safe and useful technic for skin testing with drugs were developed Most likely we are confronted here with an incomplete allergen which needs first to become more complex before reacting Is incubation of the drug with serum the answer or shall we look for other more suitable haptenic adjuvants? The solution of this problem will avoid great morbidity and mortality since drug reactions are ever on the increase

One cannot consider allergens and skin testing without mentioning even though briefly the need for identification of the allergens of the ubiquitous house dust And more important still is the urgent need to standardize the antigens used in diagnosis and treatment Despite the growth and development of allergy we as allergists can be severely criticized for using "soups" as our testing tools and each seems to be using his own brand with its own amount of seasoning

The problems raised above are of such magnitude that one national agency such as the Section of Allergy and Infectious Di

eases of the National Institutes of Health is capable of an undertaking of such magnitude as the standardization of testing materials and testing technics

The Collagen Diseases and Diseases of Autosensitivity The allergist has always been interested in these diseases but so far this has been with rare exceptions academic It has been the immunologist on the other hand who has labored and has made the greatest advances in these fields Of the collagen diseases polyarteritis nodosa is generally accepted as an allergic disease in the others in the group allergy still remains suspected but without proof (see Chap 35)

Autosensitivity as a cause of disease notwithstanding Ehrlich s contention that this was an impossibility has now been established (see Chap 6) In Hashimoto s disease we have now a classic example of autosensitivity involving the thyroid and this will undoubtedly serve as a model for detection of autosensitivity in still other diseases We know that experimentally nervous tissue the liver and testes are allergenic What is needed perhaps is the wider application of sensitive technics such as the hemagglutination test to detect this type of sensitivity

Shall the role of the allergist remain passive here? It is true that the allergist cannot use his present diagnostic technics in detecting allergy in the aforementioned diseases nevertheless his discipline which covers both internal medicine and immunology places him in the particularly fortunate position of being the bridge between these two The allergist must take a more active interest in this field—it is here that a team approach is indicated—for he can contribute much to diagnosis and therapy An approach along these lines has recently been initiated by Dr Morris Siegel of the University of the State of New York Downstate who is attacking the problem of systemic lupus erythematosus on a broad front and on a long range basis enlisting the aid of diagnosticians epidemiologists a hematologist an endocrinologist a serologist and an allergist Undoubtedly from this cooperative effort a better understanding of this baffling disease will emerge

Chronic and Intractable Asthma Chronic and intractable *asthma* is the major concern of the allergist Little progress has been made in the etiologic aspects of this condition Perhaps we are being lulled into complacency because of the efficiency of the steroids We must ever be aware that the mere alleviation of symptoms as regarding as it may be to both the patient and doctor is in reality poor practice

Why does asthma become intractable? Is it an expression of con

tinuous bacterial sensitization or are we dealing with some type of autosensitivity or self perpetuating mechanism? We have come to think over the years that perhaps asthma is a symptom complex rather than a specific disease entity This implies that mechanisms other than an antigen antibody reaction produce bronchospasm Admittedly agents other than histamine such as acetylcholine and serotonin may produce bronchospasm Perhaps we should look then for other (nonimmune) mechanisms capable of releasing these agents as the cause of some types of asthma Even if we are obstinate and insist that only histamine deserves consideration in asthma must histamine release be only on an antigen antibody basis when we have so many histamine releasing agents divers in nature and chemical composition (see Chap 4)? Should we not perhaps search more actively for histamine releasing agents in asthma and perhaps in other allergic diseases such as urticaria?

In view of the aforementioned discussion it becomes apparent that both diagnostically and therapeutically the narrow approach to allergy—strictly immunologic—is frought with frustration What is urgently needed is a broader concept and approach in which disease is considered the resultant of the interplay of many forces For more consideration of this theme the reader is referred to Chap 9

THERAPEUTIC PROBLEMS

Immunotherapy Diagnostic and therapeutic problems are conjoined Exceptionally a therapeutic measure may be applied successfully in an illness of short duration without too much concern with a specific diagnosis This is not true for most allergic diseases since they are repetitive or chronic and since specific therapy depends so much on specific diagnosis The first consideration of the allergist is then finding and removing allergens This is not always achievable and immunotherapy (hyposensitization) is therefore indicated (see Chap 56) Unquestionably this approach is successful in most instances But why do we have failures? Take hay fever for example Approximately 20 per cent of the patients who never respond to immunotherapy indicate a problem and we must search for improved therapy in this area Also disturbing is the still unsettled matter of what constitutes the best method of treatment We have advocates for high dosage and advocates for low dosage therapy (in some circles the dosage is almost homeopathic) there are those who treat only preseasonally while still others treat perennially some treat during the pollen season others discontinue some maintain a high dose others reduce In short although allergists have

used this therapeutic technic since 1911 when it was developed by Noon[3] there has been no general agreement as to what constitutes the best treatment Why this confusion? To add more fuel to the fire a single dose repository technic has again been introduced[4, 5] Based on established immunologic principles in which the antigen is retarded in its absorption this method aims to produce the de sired immunologic response with a single or few repository in jections given at one sitting The advantages in terms of the saving of time and money for the patient with this procedure are great It remains to be established however whether this procedure is as effective as the multiple dose method and whether it is safe enough to be generally employed Further discussion of this type of therapy is presented below in the review of newer therapy

As a corollary to this the mechanism involved in the relief of hay fever by immunotherapy still remains unexplained The demonstra tion of a blocking antibody by Cooke and his associates[6] and its specific identification by Loveless[7] suggested a logical explanation for the results of immunotherapy The blocking antibody was pro duced by injections of antigen and was shown to block the union of antigen and reagin by its competitive action Unfortunately there is no absolute correlation between the concentration of blocking antibody in the serum of treated patients and the results obtained and so the problem still remains[8]

The Corticosteroids One of the greatest boons to the allergist has been the demonstration of the antiallergic properties of the corti costeroids So effective are the steroids that paradoxically they gen erate problems I refer not to the side effects and complications associated with their use which are so adequately described in Chaps 31 and 57 but to its indiscriminate use in minor allergic states without adequate allergic studies and to the complacency engendered in both patient and allergist when the steroids are used for severe asthma With the patient relieved and that is after all the prime goal there is a relaxation of the search for specific causes and for specific therapy Now that newer and more potent corticosteroids have been developed (see Chap 57) and there seems to be no end of them (one wonders whether potency in itself is a worthwhile goal) there must always be the reminder that these agents are only palliative and should be used only temporarily—not routinely and not for all allergic diseases Nor should they be used in the presence of infection without adequate coverage with antibiotics

Antibiotics In the practice of allergy where infection is a major factor (see Chaps 9 18 20 21 24 27 and 52) antibiotics have be come invaluable as an adjunct to specific antiallergic therapy The

problems resulting from their use stem mainly from the necessity of their frequent application and the development of bacterial resistance The need to use them for prolonged periods of time also permits complications such as gastrointestinal irritation and superinfection with staphylococcus or monilia Furthermore some of them like penicillin are potent sensitizers The antibiotics must therefore be carefully chosen and administered Preferably they should be given after culturing the offending organisms and in some cases after performing sensitivity tests with the various antibiotics [9]

The use of single antibiotics is advocated by most physicians and this is preferable for acute infectious diseases In the practice of allergy however where we are dealing with chronic low grade infections in which the hemolytic staphylococcus is frequently encountered in my experience it is preferable to use multiple antibiotics administered as aerosols (see Chap 59) A combination of neomycin polymyxin and bacitracin so effective in topical infections of skin or eye has been found equally effective as a topical application (as an aerosol) in the respiratory tract These antibiotics are not absorbed are not sensitizing have a broad spectrum of antibacterial action and permit the withholding of the broad spectrum antibiotics when needed for specific acute infections Furthermore there is less tendency to develop bacterial resistance when several antibiotics are used in combination [10]

Drug Reactions *With the increasing use of drugs in general and of antibiotics in particular drug allergy has become increasingly vexing* (see Chap 46) In the case of penicillin as discussed in Chap 47 increasing fatalities from its use are being reported [9, 11] Penicillin has sensitized from 5 to 10 per cent of the population and accounts for 80 per cent of all drug reactions [1] This is a problem for the allergist not only in diagnosing and treating these drug reactions but in initiating prophylactic measures which is more important How to test for sensitivity safely and yet provide useful information is the major task

Some of the hemolytic reactions to drugs have been studied intensively enough to know that certain chemical forms are particularly noxious (see Chap 40) In addition where there is a family trait for a hemolytic response this has been traced to faulty hereditary enzyme metabolism [13] Perhaps this may serve as a guide to further investigation of drug allergy

Why is penicillin such a sensitizer? Is this caused by its chemical composition which may possibly be modified and made nonantigenic without altering its potency or is this caused by an inherent impaired metabolism of the patient which may be revealed by

enzymatic studies? Clarification is urgently needed in this area since fatal penicillin drug reactions are ever on the increase

Antihistamines These drugs as discussed in Chap 58 have earned a well deserved place in the therapeutic armamentarium of the allergist It should be remembered however that they have their limitations as well as usefulness certainly they are not the drug of choice in asthma and they must be specifically selected for the patient since not all respond in the same manner

In view of the broadening concept of allergy in which mediators other than histamine such as serotonin heparin and acetylcholine are considered to participate it is no wonder that antihistamines have their limitations despite the multiplicity of their pharmacologic properties They are more than just antihistaminics most have anesthetic properties and some are tranquillizers There is some inhibition of acetylcholine by the antihistamines but none for serotonin

Although many of the antihistamines share certain chemical groups which permit their classification and explain their activity some of the drugs are of such divers composition that they defy classification or explanation of their pharmacologic properties [14] Why do patients react to one antihistamine and not to another? The answer may some day be forthcoming and may perhaps be more revealing of the nature of the allergic response

Surgery The need for and extent of surgery to be employed in the treatment of infectious complications associated with asthma has always been and still remains a problem to the allergist Tonsillectomies and operations on the paranasal sinuses are performed less often now because of the increasing use of antibiotics Nevertheless we are still confronted with severe asthma associated with hyperplastic sinusitis Should these cases be treated surgically or medically relying on antibiotics? This is a question which cannot now be answered definitively The answer will come only from prolonged observation of a large group of cases treated under controlled conditions (see Chaps 27 and 54)

Psychotherapy The influence of psychiatry has been extended in medicine and thus has been felt in the practice of allergy (see Chaps 8 and 9) The position of the allergist regarding the role of the psyche in allergic disease is still in a state of flux Some admit no role for the psyche and this small group is matched by another equally convinced that the main or only approach to allergic disease is through psychiatry The truth probably lies between these opposing views the either/or approach it seems will in time give way to a blending of the two Such an attempt has been made in

Chap 9 in which an interplay of immunologic psychologic and infective forces are depicted as being involved in allergic disease

NEW HORIZONS IN ALLERGY

Newer Concepts of Allergic Mechanisms The basic theory for an allergic response—that the antigen antibody reaction releasing histamine in a specific shock organ is the sole factor—is now being challenged The histamine theory unquestionably explains most but not all of the phenomena encompassed by allergy particularly that of the immediate type (see Chaps 1 and 2) and we have recently been introduced to other mediators such as serotonin acetylcholine and heparin Serotonin seems to play a more important role in anaphylaxis in the rat and mouse while histamine is the major factor in the guinea pig [15] Since both of these amines exist simultaneously although variably in most species it may very well be that both participate in the allergic response [16] Serotonin does not seem to play a major role in asthma as encountered by the allergist except for the rare type associated with carcinoid [17]

As for acetylcholine and heparin the extent of their involvement awaits elucidation The importance of solving these basic problems cannot be overemphasized Better understanding of what goes on will unquestionably lead to better and more fundamental approaches to therapy—perhaps to corrective rather than to palliative therapy as is the mode now

Antigen antibody Complexes This phase of the allergic mechanism has recently received considerable attention in the attempt to elucidate it [18] [3] It should be noted at the outset that soluble antigen antibody complex is capable of eliciting an immediate type reaction in the nonsensitized animal [18] [19] According to Tokuda and Weiser [0] the mechanism of anaphylaxis is the same whether induced by the antigen alone in a sensitized animal or by the complex in the non sensitized

Tracer studies with iodine labeled antigen [21] have suggested that early in antibody formation antigen is present in excess and antigen antibody complexes circulate for a time until antibody formation increases at which time the complexes become increasingly larger and are removed from circulation

In one study [19] a time lag of 30 to 90 seconds was observed between the addition of the complex and the in vitro response of the uterine muscle in a Schultz Dale bath No lag was noted when histamine was used directly so it was suggested that there is a non histamine mediator The complex was most active in the range of

slight to moderate antigen excess minimal in the zone of extreme antigen excess and absent in antibody excess

In a provocative report MacHaffie Bartok and O Brien indicate that uteri previously sensitized respond more readily to antigen antibody complexes than to antigen alone These observers also concluded that histamine was not the only mediator involved and suggested possible serotonin participation

In connection with the above the work of Uhr Salvin and Pappenheimer [3] needs to be mentioned Employing insoluble antigen antibody complexes they were able to produce a delayed type of allergic reaction This has been reviewed in Chap 9

As a corollary to the above it needs to be repeated that many agents may release histamine nonspecifically without the mediation of an antigen antibody reaction (see Chap 4) This must always be borne in mind when symptoms suggestive of allergic diseases are manifested without any demonstrable antigenic cause

Shock Organ The concept of a shock organ the site of the allergic response has always interested the allergist In the past he has been content with the observation that smooth muscles are the basic shock organs This has been a satisfactory explanation for the variable anaphylactic responses in different species (see Chap 4) but does not account for other phenomena which do not involve smooth muscle spasm Perhaps we are getting closer to the truth when we consider the shock organ as an area where mast cells are concentrated It is from the mast cells that histamine serotonin and heparin are liberated [4] Narrowing the focus still further on the shock organ—or better still the site of the allergic reaction since we may not always be dealing with organs—we are beginning to think in terms of abnormal adaptive metabolic responses at the cellular level [5] involving hereditary defects (inborn errors of metabolism) disturbances of enzymatic mechanisms and the concept of molecular disease to which we now turn

MOLECULAR DISEASE ENZYMES AND HEREDITY IN ALLERGY

In Chap 9 the broad concept of homeostasis was presented It was shown that allergy which is a disordered immunologic adaptive response disturbs homeostasis and produces disease The same concept can be equally applied on a cellular or molecular level according to Pauling who conceived the term *molecular disease* The concept of molecular disease stems from the studies of Pauling and his associates of sickle cell anemia [6] In these studies it was shown that because of hereditary factors—abnormal genes—some people

were endowed with abnormal hemoglobin molecules which differed so slightly from the normal hemoglobin that special techniques such as electrophoresis were required to detect them As a result of this molecular abnormality normal metabolism of the hemoglobin molecule is impaired the enzymes normally present are unsuited for the abnormal hemoglobin and the result is sickling of cells and the train of symptoms which characterize sickle cell anemia

Another example of molecular disease of special interest to the allergist is galactosemia a disease of an inborn error of metabolism —a molecular disease—in which there is an inability to metabolize galactose Continued ingestion of galactose may result in illness varying from simple intolerance of milk (and this may be mistaken for allergy to milk) to severe illness and death The simple elimination of milk and the substitution of sucrose is sufficient to alleviate the symptoms Here a specific enzyme is necessary to metabolize a specific substrate

It is because of the specificity of allergic response and because heredity is so often implicated in clinical allergy that we must question whether allergy falls into the category of the molecular diseases Recent studies of drug and fava bean hemolytic reactions strongly suggest this Hemolytic anemia induced by naphthalene nitrofurantoin primaquine and fava bean is attributed to a metabolic abnormality of the erythrocytes characterized by a low activity of the enzyme glucose 6 phosphate dehydrogenase and a low role of incorporation of radioactive glycine into glutathione [1-3] This abnormality is hereditary and sex linked Although it may be questioned whether allergy is involved in the drug induced reactions since antibodies may not be demonstrable in the case of favism such antibodies are demonstrable Here then we have a form of allergy hereditary in origin and based on an abnormal enzyme reactions an example of molecular disease

All major biochemical reactions in the body are considered to be mediated by enzymes which function as expeditors Ultimately the allergic reaction must therefore be explained in terms of biochemical reactions The identification of the specific enzymes involved and their mode of action becomes increasingly more imperative if we are to understand allergy in its basic form Such an attempt has been made in Chap 5 Becker [11] also found that the C component of complement (four components have been isolated) so vital in hemolytic reactions was itself an enzyme an esterase In order for the hemolysis to occur however the cells had first to be sensitized It is the sensitized cell which apparently converts the pro enzyme C′ into an active enzyme ultimately resulting in hemolysis He showed

further that sensitized cells combined with C′ contained an esterase capable of splitting p toluene sulfonyl L arginine methyl ester (TAME) and that this could be inactivated by its antienzyme di isopropyl flurophosphatate The significance of this lies not only in the chemical explanation for the heretofore unexplained action of the mysterious complement but in the fact that it also opens the possibility of inhibiting certain types of allergic mechanisms by inhibiting the enzymatic processes involved [31]

Ungar[3] has also reported that antigen antibody reactions release proteinases—again the enzymes

In view of the foregoing it is now necessary to achieve the ultimate in explaining allergy namely to bridge the gap between the allergic mediators (histamine serotonin heparin and perhaps acetyl choline) and the enzymes involved *

In recent reports evidence has been presented that complement is directly involved in cellular damage associated with allergic reactions This view is expressed in Chap 38 to account for allergic damage to kidney cells If ways can be found to prevent or modify this action of complement then perhaps we can prevent such damage to cells and avoid irreversible allergic reactions This is a challenging goal for the research worker in the field of allergy

One cannot leave the discussion of enzymes without mentioning their role in inducing itching This is a particularly troublesome symptom the relief of which would go a long way in ameliorating allergic disorders Following the observation of Broadbent[34] that the itching normally induced by itch powder (cowhage) could be prevented by boiling of the powder Shelley and Arthur[3] began a search for the agent responsible and found it to be a proteinase mucunain These investigators subsequently found that in atopic dermatitis the itching response to mucunain and to trypsin was greater (in terms of itch sensitivity and time of itch) than that noted in contact dermatitis or in normal skin These observations will undoubtedly lead to further studies explaining the reaction of atopic skin—is it lacking in some enzyme?—and possibly to therapy with specific antiproteinases

ANTIGENS COMMON TO FOODS AND INHALANTS

An intriguing observation in which common allergens are reported in both foods and inhalants has been reported by Pisani[36] and deserves the attention of the allergist This should be either

* An excellent review of the development of enzyme systems as encountered in early infancy has recently appeared in a supplement of Pediatrics[illegible]

confirmed or rejected by other investigators in the near future Acceptance of this observation would ultimately lead to special diets for the hay fever patient Perhaps the failures in the treatment of hay fever previously mentioned may be accounted for in this manner Perhaps here we are also dealing with an enzymatic failure resembling that of galactosemia previously discussed which would also require special dieting for its relief

Agammaglobulinemia and Allergy Disturbances in globulin formation must of necessity reflect itself in increased susceptibility to bacterial infection and to a modification of the host response to antigens since gamma globulin is so intimately associated with antibody production Indeed it was the study of patients who were unusually vulnerable to infection and the attempt to explain their lack of immunity that led to the discovery of this unusual disease[37]

Agammaglobulinemia congenital or acquired is a disease of protein metabolism in which the patient cannot respond to antigenic stimulation by the usual production of plasma cells antibodies and gamma globulin The allergist has therefore an unusual interest in agammaglobulinemia since theoretically the absence of gamma globulin (or its marked reduction which is really the case) should be associated with the absence of allergy Goode and associates[48] have investigated this problem and have shown that although the immediate type of allergy is absent the delayed type is occasionally present or can be induced with 2 4 dinitrofluorobenzene

The patient with agammaglobulinemia has been a heaven sent walking laboratory to the immunologist Here nature has provided a state which could not be duplicated experimentally Intense study of these patients has revealed that although there is failure of immunity against infection this seems to apply only to bacterial infection Surprisingly patients with agammaglobulinemia tolerate viral infections very well This poses the question whether different types of defense mechanisms are brought into play by different types of infectious agents

More pertinent to allergy was the observation that heterologous tissue transplants (skin grafts) are not readily rejected by patients with agammaglobulinemia This supports the concept that an allergic mechanism mediates graft rejection That this is an allergic response is generally accepted This concept and related matters are considered below

Tissue Transplantation It is well known that the grafting of tissues or organs is fraught with difficulty Only in identical twins (monozygotic) can transplants be assured of a successful take It has only been in recent years however that the immunologic or allergic

mechanism involved has been demonstrated The support for an immune mechanism in graft rejection stems from (1) the ability to homograft in cases of agammaglobulinemia and in the embryo or at birth when no antibody formation occurs (2) the latent period before the first graft is rejected—it is the time required to produce antibodies (3) the accelerated rejection of a second graft from the same donor (4) the effect of prior sensitization of the host by injection of donor cells in which the first graft behaves like a second and is rejected quickly and (5) sensitized cells of the leukocytic series transferred from a grafted animal to a normal animal transfer immunity so that a first transplant from the same donor behaves like a second and is rejected rapidly[39]

Antibodies toward foreign proteins (whether in the form of cells tissues or organs) may exist prior to grafting This is illustrated by the normal presence of antibodies of the iso type against blood cells of other species or against blood groups of the same species On the other hand antibodies may develop only on exposure of the host to the graft In general the allergic response in graft rejection resembles that of the delayed type as illustrated in Table 51[40]

TABLE 51 ANALOGIES BETWEEN TUBERCULIN TYPE HYPERSENSITIVITY AND HOMOGRAFT REJECTION

	Tuberculin type hypersensitivity	Homograft rejection hypersensitivity
Induction of sensitivity	Intact bacterial cells	Intact tissue cells
Latent period	10–14 days	10–12 days
Result of challenge	Koch phenomenon	Accelerated rejection
Specificity	For specific bacterium	For specific donor
Presence of measurable serum antibody	Variable	Variable
Parallelism between degree sensitivity and serum antibody	Not demonstrated	Not demonstrated
Transfer of sensitivity with serum	Negative	Negative
Transfer of sensitivity with cells	Positive	Positive
Cytotoxicity of antigen for explanted cells	Present	None

SOURCE After Lawrence Ann N Y Ac Sci 59 896 (1957)

It has been shown that grafting even heterologous can be successful during the embryonic state of the host or shortly after its birth[41] Apparently antibody formation in some species does not occur until some time after birth and this accounts for the successful transplants Although the embryo is incapable of producing anti

bodies it does have an immune response not based on antibodies which is called the tolerance response phenomenon about which more will be said later

In the usual graft host relationship it is the host which reacts to the graft and finally destroys it by antibody production The reverse can also be observed under certain conditions If adult spleen is grafted on the newly born chick and the contact is maintained long enough it will destroy the host[4] This is the graft against host reaction and can be produced by any tissue of reticuloendothelial origin Since this tissue is capable of producing antibodies and since the host at this stage cannot the host is destroyed This phenomenon is important clinically whenever bone marrow is injected for the purpose of rejuvenating blood cell formation Now that radiation injury and its effect on blood formation has assumed such great importance it is imperative that the dangerous aspects of bone marrow injections be understood so that they may be avoided since this is the indicated therapy Indeed where prolonged radiation therapy is anticipated it has been advocated that marrow be removed from the patient prior to treatment stored in the frozen state and re injected into the patient following the radiation therapy[43] This avoids the dangers of an adverse graft against host reaction particularly where the host s antibody formation is weak as after radio therapy

The Tolerance Response Phenomenon As previously mentioned the failure of the embryo or newborn to reject a graft because of its incapacity to produce antibodies is called the tolerance response phenomenon[41] This is not mediated by antibodies but is nevertheless a changed reactivity of the embryo or the newborn to an antigen This according to Billingham[44] is illustrated by the red cell chimeras in which two different types of red cells can be found in cattle because of intermingling of the blood stream of nonidentical twins in utero

Cells from a donor injected into newborn mice permit skin grafting later from the same donor without its rejection by the pretreated host This tolerance of a similar graft cannot be observed in the un treated mice serving as a control

We cannot with rare exceptions such as hereditary kidney mal formation anticipate the need for grafts later in life and modify the host at birth by suitable injections However in understanding the mechanism which produces tolerance we may perhaps ultimately achieve this type of response in the adult—perhaps this may be accomplished during a period of temporary suppression of antibody Skin grafting at times may be life saving more so in the grafting of

vital organs to replace those diseased The surgical technics are available we need only to hurdle the immunologic obstacle which is no simple task

The tolerance response phenomenon also explains why animals do not normally react to their own tissues tolerance is developed to these tissues during the course of development Only tissues such as sperm lens brain skin and thyroid which are separated by capsule or other anatomical means from the rest of the baby a kind of physiologic quarantine are capable of producing antibodies of the auto type (see Chap 6) Waksman[45] indicates that the auto type of response is mesodermal and against ectodermal and endodermal tissue

In the aforementioned discussion lies an explanation for diseases of autosensitivity It follows from this that modified body protein achieved by whatever means (bacterial chemical degenerative changes etc) would be considered by the body as foreign and would produce antibodies against it and initiate an allergic response This is a variation of autosensitivity and may perhaps account for the collagen and related diseases Perhaps the modified cancer cell is sufficiently altered to become antigenic? To this we now turn our attention

CANCER AND ALLERGY

There are two aspects of the relationship between cancer and allergy which deserve consideration The first concerns the observation of an immune mechanism in the experimental grafting of malignant tumors This involves a donor host relationship of an unusual type in which immunity is associated with enhancement of growth of cancer tumors Kaliss[46] who has investigated the problem has shown that unlike graft rejection homografts transplantable tumors survive in mice (normally nonreceptive to this tumor) that are pretreated with normal mouse spleen kidney or liver In mice receptive to a specific tumor transplant a second transplant of the same tumor may grow more rapidly than the first Again instead of an immune response leading to rejection the opposite was observed

Where a tumor had a 50 per cent rejection rate in a specific strain of mice and if pretreatment was made with a small inoculation of the freeze-dried homologous tumor tissue immunity was noted a larger inoculation led to its abrogation Furthermore antiserum to mouse tissues (produced in rabbits) when inoculated into the prospective host prior to tumor grafting ensures the survival of the tumor homograft in mice

These observations indicate that this phenomenon is not due to a growth stimulating factor produced by the growing tumor It is an

immune reaction associated with antibody contained in the globular fractions of the antiserum as employed above

How then can we explain the paradoxical reaction of immunity leading to tumor acceptance rather than to the anticipated rejection? The question raised is not purely academic since understanding of this phenomenon (enhancement or conditioning) may solve the problem of homotransplant rejection Kaliss accounts for the ultimate acceptance on the basis of an interplay of two opposing forces a homograft rejection force mediated through lymph node activity involving hemagglutonins and the opposing antiserum factor The latter ultimately overcomes the former In addition the antigen of the tumor during its growth undergoes change losing some of its antigenicity

The second relationship of cancer and allergy implies an allergic reaction to a foreign protein contained within the cancerous tissue This is the contention of Makari[4] who developed a Schultz Dale test *for detecting antigens in the sera of patients with neoplastic disease* this has been confirmed by Burrows[49] Makari believes the allergen to be a polysaccharide The test is performed by sensitizing female guinea pigs with homogenates of cancer tissue along with Freund s adjuvant The excised horns of these uteri are used in the Schultz Dale reaction with the contraction of the muscle serving as the indicator Since the homogenates used in sensitization contain both normal and cancerous cells the uteri are first exposed to normal serum and thereby desensitized to normal cells This is then followed by the addition of serum to the bath from the cancer suspect Contraction when exposed to serum from a cancer patient then presumably occurs only to the cancer antigen Makari reports 96 8 per cent positive reactions in carcinoma compared with 4 8 per cent in noncancerous diseases making this a specific diagnostic test for carcinoma Burrows reports similar findings

It should be pointed out that although the Schultz Dale technique is highly sensitive for detecting antibodies it has its limitations—it cannot be subjected to quantitative procedures as in the case of gel diffusion for example Furthermore the test is time consuming particularly in inducing sensitization in the guinea pig

Makari[49] has also developed a skin test using polysaccharide antigen obtained from cancerous tissue Direct testing with the antigen in saline solution gives an immediate reaction which indicates immunity and is similar to the reaction of Francis and Tillet[50] produced with pneumococcal polysaccharide in pneumonia On the other hand when the antigen is first incubated with the patient s serum producing an antigen antibody complex a positive skin test

reveals the presence of autoantibodies and indicates either suscepti bility to cancer or the disease itself

Should this test be verified and found suitable for skin testing by the general practitioner a valuable tool would then become generally available for diagnosis and for screening purposes

DIAGNOSTIC TECHNICS

Many new diagnostic tests have been developed to detect various types of allergic responses These have received special consideration in Chap 15 Although they are primarily refined tools for the in vestigator and are designed primarily for basic research some have become useful tools in practice This is particularly true for the highly sensitive hemagglutination test which has been used to detect the autoantibodies in Hashimoto s disease Modification of the ag glutination reaction by the use of coated latex[51] or bentonite par ticles[5] have provided simple and refined techniques for the diagnosis of the rheumatic factor in rheumatoid arthritis There is always the urgent need to bridge the gap between the investigator and the clinician This is particularly evident in allergy where there are so many useful tests for the experimenter but only a few suitable for the clinician

NEWER THERAPY

In view of the newer knowledge available about allergic disease new approaches to therapy must be anticipated Perhaps the most fruitful for the future lies in the realm of enzymes

Enzymes Enzyme therapy for the future may conceivably be di rected along the following lines (1) modification or destruction of the allergen by a suitable enzyme (2) modification of the allergic reaction (presumably due to proteinases) by the administration of anti proteinases and (3) modification where possible of the allergic reaction by correction of inborn errors of metabolism This implies the provision of absent or deficient enzymes or the elimination of substances (amino acids) unsuitable for the host s pattern of enzymes (as in galactosemia or phenylketonuria)

Although the aforementioned sounds visionary and at first glance might be dismissed as a form of daydreaming some of this has al ready been achieved We are currently using an enzyme (penicil linase) to destroy its substrate in cases of chronic penicillin allergy or where a vaccine containing the drug may have to be given to patients known to be sensitive[1] We have also applied enzymes to horse serum proteins modifying their chemical structures (despeciat

ing) without destroying the antibody so that they are not allergenic for the horse serum sensitive patient

Although we have no example in food allergy comparable to phenylketonuria or galactosemia where there is definite error of metabolism and which is readily corrected by elimination of unsuitable substrates in food it is conceivable that this may ultimately find application in allergy (Perhaps when we eliminate certain foods found to be detrimental to patients we are not eliminating so much an allergen as a food for which the body has not the right enzyme for metabolism)

More likely as the allergic mechanism is better understood and becomes translated into enzyme reactions (probably involving a series) suitable antienzymes will find their way into practice to counteract the adverse effect of the enzymes released by the antigen antibody reaction This is foreshadowed by the work of Becker (see Chap 5) who has been able to inhibit the esterase (complement) involved in the lysis of sensitized red blood cells by the use of an antiesterase (An identical approach is receiving concentrated attention in psychopharmacology where the monoamine oxidase acting on serotonin and norepinephrine is being inhibited by antienzymes to increase the concentration of these amines in the brain thereby restoring normal brain function)[53]

Histamine releasing Agents A variety of agents have now been identified which are capable of releasing histamine from their intracellular stores without the mediation of an antigen antibody reaction This has been discussed by Halpern in Chap 4 He has also applied one of these L 1935 clinically to patients suffering from chronic urticaria He depletes these patients of their histamine with the injection of L 1935 controlling the symptoms in the meantime with antihistamines Since it takes a period of time to reform the normal concentration of histamine (about five days) the patients presumably have a histamine free period during which no allergic reaction can take place This free period can be lengthened by the administration of cortisone which inhibits histamine formation Thus far Halpern has limited his studies to patients with urticaria in whom histamine is more certain to play a positive role and in whom the histamine artificially released does not ordinarily endanger life

LeComte[54] in an intensive study of L 1935 administered intravenously to nonallergic patients demonstrated an apparent release of histamine Depending upon the dose and speed of injection different reactions were encountered from simple flushing to intense anaphylactoid reactions Following the initial injections refractory

periods of up to five days were noted In view of the dangers involved in its use it is doubtful whether L 1935 and similar agents will become suitable for general use in allergic practice

Since there seem to be so many agents which release histamine it is conceivable that a counterpart to this a histamine binding agent may some day be discovered This it seems would be a more desirable agent for therapy Perhaps this too belongs in the field of enzymology

Corticosteroids Nowhere has the science of chemistry excelled itself as in the field of corticosteroids rearranging atoms and manipulating the basic structure of cortisone so that markedly improved and highly potent compounds have now been synthesized (see Chap 57) The temptation to use these steroids becomes increasingly great now that we have them in more potent form and largely devoid of the major side effects of the progenitor Since there is little concern about hypertension diabetes and (salt retention) edema with the newer steroids there is less hesitancy to use them They are palliative only however and they are not yet completely devoid of troublesome side reactions We must anticipate then efforts at producing the perfect steroid for allergic disease thereby increasing the danger of being lured away from the main goal the finding and *removing of allergens or when necessary immunizing the patient* into modifying the allergic state The steroids rightfully should be used only for short term therapy Their prolonged use indicates a defeat for the physician and that further investigation of the disease state is needed rather than a search for newer miracle drugs

Repository Injections of Antigens Mention was made earlier about the inadequacies of the present methods of hyposensitization therapy in the practice of allergy Too many injections have to be given and at times with unrewarding results Yet injection therapy has proved fruitful in the majority of patients The single repository injection advocated recently by Loveless [4] offers the possibility of circumventing the time factor without jeopardizing the results The method however needs to be improved The ophthalmic tests involved in the case of pollinosis are cumbersome reactions of various degrees of severity are encountered (often hours after the injection) [5] abscesses at the site of injection have been reported (sterile and infected) lumps at the site of injection remain for long periods of time particularly with house dust [5] and one wonders about the carcinogenic properties of the mineral oil injected These are obstacles however that can and will be hurdled in the future The principle is correct the refinements (testing dosage prevention of reactions) will come in time Perhaps we can also anticipate a large dose given in a single injection to be followed by smaller booster

injections at infrequent intervals to maintain the immunity More research in this area is indicated before repository injections can be generally employed this must be done cautiously by qualified workers

Tracheotomy What are the indications for this procedure and has it a place in the practice of allergy? There can be no question about its indication in cases of angioedema involving the glottis Here it may be life saving (see Chap 61) It can be questioned however whether this procedure can be helpful in severe status asthmaticus as suggested by Loveless It would seem impossible for any mechanical approach to empty the terminal bronchiates of their tenacious plugs as found in asthma Temporary tracheotomy has been life saving in respiratory paralysis following poliomyelitis permitting removal of obstructive mucus presumably the same approach for the same reason—removal of obstructive mucus—would therefore be indicated in status asthmaticus Not enough clinical experience has been had with this procedure however to give it unqualified endorsement

More intriguing to the allergist is the possibility of utilizing permanent tracheotomy (tracheal fenestration) for some types of asthma The procedure was introduced by Mayer Blazsick and Rappaport[5] as a last desperate procedure for extreme pulmonary insufficiency and has been surprisingly successful This surgical technic was perfected by Rockey[58] Since the patient is taught ultimately to catheterize his bronchi and to drain them it may possibly find a useful place in bronchial asthma which is unresponsive to medical therapy and associated with advanced emphysema and marked pulmonary insufficiency

THE OVER ALL APPROACH

Mentioned earlier in this book (Chap 9) and in the introduction to this chapter is the interrelationship of allergy infection and the psyche It is fitting in the final words of this book to stress again the importance of seeing the clinical problem (the patient) in toto —the importance of avoiding compartmentalization treating instead the whole patient not just his allergies utilizing antiallergic anti infective and psychotherapeutic measures together as indicated

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APPENDIX I

Margaret B Strauss

THE PREPARATION OF ALLERGENIC EXTRACTS FOR TESTING AND TREATMENT

THE PURPOSE OF PREPARING EXTRACTS

The skin test is the outstanding specific diagnostic procedure in clinical allergy It represents an effort to utilize in a controlled localized and wholly circumscribed way the general allergic mechanism which is activated when the sensitized person is thrown into contact with the specific exciting substance In both the intracutaneous test and clinical reaction the allergic antibody present in the tissues is exposed to an antigen of foreign origin in the one instance in the vehicle of a prepared extract in the other in the clinical environment Therefore the more completely the antigen in extract form retains the characteristics which it possesses in its natural state in the environment the more precise and the more accurate the intracutaneous test will be Indeed it would be ideal if it were possible to perform the tests with the antigens in their natural fresh state or original condition Since this is manifestly impossible except in occasional instances the attempt must be made to obtain a testing product which retains for a considerable period of time the antigenic characteristics of the raw materials

REQUIREMENTS FOR A DEPENDABLE EXTRACT

It is relatively easy to prepare an extract with a high initial potency it is more difficult to make one that will retain its activity after months of storage To qualify as satisfactory therefore an extract must not only contain the specific antigenic substance in active form it must maintain a high level of potency over periods of months it must be sterile its pH must be adjusted so that it is non irritating and painless when introduced into normal tissues it must lend itself to standardization and it must be in such a physical form that it can be utilized conveniently and without discomfort in the intracutaneous test and subcutaneous injection for treatment The following procedures have been devised with these prerequisites in mind

I PROCEDURES IN GENERAL

A Grinding pulverizing blending For optimum extraction crude antigens except pollens should be reduced into as fine a particulate form as is practical Dry materials such as grains and seeds are pulverized in a coffee grinder Most bulky moist foods such as meats fish vegetables fruits also nuts to bacco and pyrethrum flowers are chopped finely in a meat grinder or an electric blender

B Elimination of fats and oils All antigenic materials except fruits and vegetables are treated with an organic solvent to remove fats and oils

Pollens are treated with ether which has the disadvantages of being highly inflammable very volatile and expensive Pollens are washed three times to remove the greater part of the oil in the pollen grain since the oil fraction has not been thought generally to contain any necessary antigenic material and its removal results in a clear aqueous extract Pollens must be free of solvent and absolutely dry before aqueous extraction Recently however Fuchs and Strauss[1] have suggested that nondefatted pollen be used in a special extraction and precipitation of the active complex since denaturization and splitting of an active pollen fraction may be caused by defatting and dehydrating with ether *All other materials* except meats fish nuts and fresh fruits and vegetables may be extracted with toluene or with Sovasol #5

Meats fish and nuts are treated with three washings of acetone which is not only an efficient fat solvent but in contrast to toluene and Sovasol mixes in all proportions with

water and therefore dehydrates as well The material is squeezed through several layers of gauze before fresh solvent is added to it It is important to filter each portion of organic solvent used before it is discarded in order to reclaim any finely divided or powdery portion of antigen which otherwise might be lost The acetone should be removed from the de fatted material by thorough evaporation at room tempera ture before aqueous extraction is attempted

Other dry antigenic materials to be extracted are com pletely covered with the toluene or Sovasol solvent and are thoroughly mixed at intervals and the colored solvent re moved by decantation or filtration Fresh solvent is then added repeating the mixing or the extraction may be con tinued overnight

C *Extraction with aqueous solvent with or without adjuvants* In general four types of extracting fluids are used in the preparation of allergenic extracts

1 Alkaline extracting fluid so-called Coca s solution has a pH of 8 2 It is used to extract all pollens dusts and molds because these antigens are initially quite acid The bicarbonate in Coca s solution is better able to maintain a a neutral pH after extraction with these acid antigens The other extracting fluids would turn acid after extrac tion with these antigens and a much less potent extraction would be obtained with them
2 Buffered saline [3] pH 7 0 is used to extract most other anti genic substances except those in which it is necessary to include a reducing substance in the extraction me dium
3 Buffered sodium formaldehyde sulfoxylate (SFSO) extract ing fluid [4] has a pH of 7 4 It is used to prevent the forma tion of black oxidative pigments in the final extract
4 A five fold concentration of buffered saline or buffered SFSO Four parts of the fruit or vegetable juice are added to one part of one of these concentrated extracting fluids to prevent undue dilution

The composition of these extracting fluids is as follows

a Alkaline extracting fluid pH 8 2 described by Coca

Sodium chloride (NaCl)	5 0	Gm
Sodium bicarbonate ($NaHCO_3$)	2 75	Gm
Phenol (C_6H_5OH)	4 0	Gm
Distilled water q s	1 000	ml

b Buffered saline pH 7 0 suggested by A Evans

Potassium phosphate ($KH\,PO_4$)	0 363 Gm
Sodium phosphate ($Na\,HPO_4\,12\,H\,O$)	0 431 Gm
Sodium chloride (NaCl)	5 0 Gm
Phenol	4 0 Gm
Distilled water q s	1 000 ml

c Buffered sodium formaldehyde sulfoxylate extracting fluid pH 7 4 described by Strauss and Spain

Potassium acid phosphate ($KH\,PO_4$)	2 725 Gm
1 normal sodium hydroxide	15 73 ml
Sodium formaldehyde sulfoxylate	10 00 Gm
Distilled water q s	1 000 ml

d Concentrated sodium formaldehyde sulfoxylate extracting fluid (a five fold concentration of #3) concentrated buffered saline (a five fold concentration of #2)

The list below shows the allergens to be extracted in the various extracting fluids and the approximate weight by volume extraction for a potent extract for testing and treatment Since standardization by nitrogen determination is carried out as the final step in the preparation of these extracts the proportion of antigen to extracting fluid need not be accurately measured

Extracts containing 50 per cent glycerine[5, 6] have the advantage of remaining stable for at least five years whereas aqueous solutions without glycerine deteriorate at a much more rapid rate However an extract must contain at least 50 per cent glycerine to maintain stability and this concentration is highly irritating and painful upon injection Unless a very concentrated stock extract can be prepared which can be diluted at least five times before use for testing or treatment in order to cut the glycerine to 10 per cent it is not advisable to use a glycerinated extract

Because of the increased viscosity of a 50 per cent glycerinated solution over an aqueous fluid for extraction a poorer extraction of antigenic material by a 50 per cent glycerinated extracting fluid is obtained It is therefore best to extract initially in an aqueous extracting media Concentrate this extract several fold and then add an equal volume of glycerine It should also be noted that if extraction is made in 50 per cent glycerinated solutions concentration is not feasible

D *Dialysis* All extracts are dialyzed except those of pollen milk egg and horse serum Cellophane sausage tubing is the semipermeable membrane used for dialysis This grade of

1 Allergens extracted with alkaline extracting fluid (Coca s) Pollens To obtain at least a 20 000 unit extract the following weights of pollen are used per 100 ml of extracting fluid

Beech birch poplar	8 Gm
Ash elm oak hickory	5 Gm
Timothy orchard ragweed	5 Gm
Plantain	8 Gm

Fungi 5 Gm of dried powdered fungi per 100 ml

Dust Only sufficient extracting fluid to moisten

2 Allergens extracted with buffered saline (sufficient to cover with exceptions noted)

Apricot	Cornmeal (1 Gm 5 ml)	Parsnip
Barley (1 Gm 5 ml)	Epithelia	Pea (green)
Beans (lima string)	Fig	Pumpkin
Broccoli	Horseradish	Rice (1 Gm 5 ml)
Brussels sprouts	Nuts (1 Gm dry and defatted 10 ml)	Silk
Carrots	Okra	Soybean meal (1 Gm 5 ml)
Cauliflower	Oyster plant	Squash
Corn	Parsley	Turnip

3 Allergens extracted with concentrated buffered saline (to 4 parts of juice add 1 part of concentrated buffered saline)

Cabbage	Grape	Pineapple
Cantaloupe	Grapefruit	Rhubarb
Cucumber	Honeydew melon	Tangerine
Currant	Lemon	Tomato
Garlic	Lime	Watermelon
Gooseberry	Onion	Watercress
	Orange	

4 Allergens extracted with buffered sodium formaldehyde sulfoxylate fluid (sufficient to cover except where otherwise indicated or marked with J — J signifies juicy to 4 parts of juice add 1 part of concentrated sulfoxylate fluid)

Alligator pear	Dandelion J	Pear J
Apple J	Date	Pepper (green and red)
Artichoke	Eggplant J	Plum J
Asparagus J	Endive J	Potato (sweet and white)
Banana	Fish (1 Gm dry and defatted 10 ml)	Prune
Bean (Navy)		Pyrethrum (1 Gm 5 ml)
Beef	Flaxseed (1 Gm 20 ml)	Radish
Blackberry J	Huckleberry	Raisin
Blueberry J	Kapok seed (1 Gm 10 ml)	Raspberry J
Buckwheat (1 Gm 5 ml)	Lettuce J	Rye (1 Gm 5 ml)
Celery J	Meats (1 Gm dry and defatted 10 ml)	Spices (1 Gm 5 ml)
		Spinach J
Cherry J	Mushroom	Strawberry J
Chocolate (1 Gm 5 ml)	Oats (1 Gm 5 ml)	Tea (1 Gm 5 ml)
Coffee (1 Gm 5 ml)	Olives (green and ripe)	Tobacco
Cottonseed (1 Gm 10 ml)	Orris (1 Gm 5 ml)	Vanilla
Cranberry	Peach J	Wheat (1 Gm 5 ml)

Epithelia (cat dog chicken etc) are listed as a group and not separately
Meats and fish are listed in groups and not separately

b Buffered saline pH 7 0 suggested by A Evans

Potassium phosphate (KH_2PO_4)	0 363 Gm
Sodium phosphate ($Na_2HPO_4 \cdot 12H_2O$)	0 431 Gm
Sodium chloride (NaCl)	5 0 Gm
Phenol	4 0 Gm
Distilled water q s	1 000 ml

c Buffered sodium formaldehyde sulfoxylate extracting fluid pH 7 4 described by Strauss and Spain

Potassium acid phosphate (KH_2PO_4)	2 725 Gm
1 normal sodium hydroxide	15 73 ml
Sodium formaldehyde sulfoxylate	10 00 Gm
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d Concentrated sodium formaldehyde sulfoxylate extracting fluid (a five fold concentration of #3) concentrated buffered saline (a five fold concentration of #2)

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D *Dialysis* All extracts are dialyzed except those of pollen milk egg and horse serum Cellophane sausage tubing is the semipermeable membrane used for dialysis This grade of

1 Allergens extracted with alkaline extracting fluid (Coca's) Pollens To obtain at least a 10 000 unit extract the following weights of pollen are used per 100 ml of extracting fluid

Beech birch poplar	8 Gm
Ash elm oak hickory	5 Gm
Timothy orchard ragweed	5 Gm
Plantain	8 Gm

Fungi 5 Gm of dried powdered fungi per 100 ml

Dust Only sufficient extracting fluid to moisten

2 Allergens extracted with buffered saline (sufficient to cover with exceptions noted)

- Apricot
- Barley (1 Gm 5 ml)
- Beans (lima string)
- Broccoli
- Brussels sprouts
- Carrots
- Cauliflower
- Corn
- Cornmeal (1 Gm 5 ml)
- Epithelia
- Fig
- Horseradish
- Nuts (1 Gm dry and defatted 10 ml)
- Okra
- Oyster plant
- Parsley
- Parsnip
- Pea (green)
- Pumpkin
- Rice (1 Gm 5 ml)
- Silk
- Soybean meal (1 Gm 5 ml)
- Squash
- Turnip

3 Allergens extracted with concentrated buffered saline (to 4 parts of juice add 1 part of concentrated buffered saline)

- Cabbage
- Cantaloupe
- Cucumber
- Currant
- Garlic
- Gooseberry
- Grape
- Grapefruit
- Honeydew melon
- Lemon
- Lime
- Onion
- Orange
- Pineapple
- Rhubarb
- Tangerine
- Tomato
- Watermelon
- Watercress

4 Allergens extracted with buffered sodium formaldehyde sulfoxylate fluid (sufficient to cover except where otherwise indicated or marked with J — J signifies juicy to 4 parts of juice add 1 part of concentrated sulfoxylate fluid)

- Alligator pear
- Apple J
- Artichoke
- Asparagus J
- Banana
- Bean (Navy)
- Beef
- Blackberry J
- Blueberry J
- Buckwheat (1 Gm 5 ml)
- Celery J
- Cherry J
- Chocolate (1 Gm 5 ml)
- Coffee (1 Gm 5 ml)
- Cottonseed (1 Gm 10 ml)
- Cranberry
- Dandelion J
- Date
- Eggplant J
- Endive J
- Fish (1 Gm dry and defatted 10 ml)
- Flaxseed (1 Gm 10 ml)
- Huckleberry
- Kapok seed (1 Gm 10 ml)
- Lettuce J
- Meats (1 Gm dry and defatted 10 ml)
- Mushroom
- Oats (1 Gm 5 ml)
- Olives (green and ripe)
- Orris (1 Gm 5 ml)
- Peach J
- Pear J
- Pepper (green and red)
- Plum J
- Potato (sweet and white)
- Prune
- Pyrethrum (1 Gm 5 ml)
- Radish
- Raisin
- Raspberry J
- Rye (1 Gm 5 ml)
- Spices (1 Gm 5 ml)
- Spinach J
- Strawberry J
- Tea (1 Gm 5 ml)
- Tobacco
- Vanilla
- Wheat (1 Gm 5 ml)

Epithelia (cat dog chicken etc) are listed as a group and not separately
Meats and fish are listed in groups and not separately

cellophane is well suited for this purpose since it retains the larger molecules with which the activity of the extract is associated allowing the electrolytes a large amount of coloring matter and lower molecular nonspecific irritating substances to dialyze out Many extracts overrun the buffer capacity of the extracting fluid during extraction and are acid Dialysis is therefore continued until the diffusate maintains its initial pH after 24 hours of dialysis

Procedure A suitable length of cellophane tubing is cut from the roll At one end of the tubing a double fold is made which is pleated together and tied securely with string The extract is introduced into the casing from the other end and a thin layer of toluene is added to check bacterial contamination The sides of the casing above the liquid are then flattened together with the fingers displacing most of the air This end of the casing is then sealed in the same way as the other end The casing is placed in a fairly large sized jar which is filled with buffered saline or buffered sodium formaldehyde sulfoxylate (SFSO) extracting fluid The extracts which were extracted with buffered SFSO extracting fluids are dialyzed against buffered SFSO pH 7 4 All other extracts are dialyzed against buffered saline The buffered saline or SFSO is changed every 24 hours until its original pH is maintained after a 24 hour period of dialysis The pH is checked by the use of Squibb s nitrazine pH indicator paper

E *Concentration of extracts* Some extracts must be concentrated in order to obtain satisfactory testing and treating strengths or in order to obtain very concentrated extracts which may be diluted in equal volume with glycerine for stabilization These are the fruits vegetables epithelia dusts meats fish nuts seeds and grains Pollens are not concentrated The dialyzed extract in the cellophane casing is hung from a line before an electric fan The extract may be concentrated to any desired volume by evaporation through the membrane

F *Sterilization of extracts* After the preliminary filtration of an extract which is done in order to separate it from the mass of crude material with subsequent dialysis concentration and ordinary paper filtration where indicated the pH of the extract is again checked to make certain that it is neutral Dilute NaOH solution is added until a pH of 7 0 is reached if the extract is acid The next step is to insure freedom of the product from bacterial or fungal contamination Sterilization by the addition of chemicals is undesirable since nonspecific

irritation may result from them. The use of heat is contraindicated since it destroys the antigenic activity. Sterilization by the mechanical removal of contaminants, that is, bacterial filtration, is necessary.

There are several types of bacterial filters in general use. The Seitz filter is the one recommended since its filtering surface consists of a specially packed asbestos pad of such fine porosity that bacteria are not able to filter through. The pad is discarded after one filtration and it is inexpensive to replace. The two metal parts of the Seitz filter are washed with a soft cloth and mild soap, rinsed well and dried. A piece of regular filter paper is placed beneath the asbestos pad when it is assembled for sterilization to prevent lint from the asbestos from passing into the extract.

The Selas filter consists of a porcelain thimble of various sizes, the bottom edges of which are sealed to a porcelain funnel. These Selas filters may be cleaned with cleaning solution, thoroughly washed to neutralize, or may be placed in a muffle furnace and any antigenic material is burned off.

A definite quantity of active material in the extract is absorbed by the asbestos pad of the Seitz filter. It is therefore advisable to use a smaller size filtering cup and pad when smaller quantities of extracts are filtered to reduce proportionally the amount of activity which is lost by adsorption. The 100 ml. and 25 ml. Seitz filter cups have been found adequate to cover most cases. Large size Ertel filters (Seitz type) are useful for the filtration of over 2 l. of extracts. Large size Selas candles are useful for sterilization of large quantities of buffered saline for use in diluting and result in lint free solutions.

When very small quantities of extracts (2 to 15 ml.) need bacterial filtration (especially in the office when there is any question of contamination caused by the presence of a cloudy extract) a micro type of Seitz filter is more opportune. There is a Swinney Filter Adapter which utilizes a Luer-Lok Syringe to which pressure is applied by hand to force the liquid through the filter. The Hemmings Filter is a new English microfilter utilizing the centrifugal force to push the liquid through the filter. It is most efficient and time saving.

Extracts must be kept at ice box temperature (5C.) except when in use, since they deteriorate at a much greater rate at room temperature.

C. Sterility tests. The Seitz filtration procedure ...

tain amount of antigenic activity from an extract Therefore before any attempt at standardization of potency is made sterility should be confirmed as any refiltration made necessary by contamination would again change the activity of the extract Tests for sterility are made 24 hours after the extracts are bottled both aerobic and anaerobic cultures being necessary

The extract is transferred with a sterile pipet into duplicate culture tubes containing thioglycolate media This media which sustains the growth of both aerobes and anaerobes is obtainable in powdered form and need only be dissolved in water and sterilized The anaerobic culture is important since it is possible that pollens epithelia and grains could carry spores along with them if improperly filtered The cultures are incubated at 37C for one week A positive culture is indicated by a cloudy media If contaminated the extract must be refiltered through a Seitz or Selas filter

H *Standardization* There are three standards in common usage This is unfortunate in that there is always some confusion when a physician has to treat a new patient previously maintained on a dosage expressed in units different from his own and the dosage must be converted to his standard unit As a safety measure the dosage should be dropped one third when changing from one extract as described to another

1 The weight by volume (w/v) method of standardization described by Noon is based upon the weight of dry antigen in the total amount of extracting fluid There are many variables when this method of standardization is employed

First the actual amount of antigenic material may vary considerably from one batch of antigenic mass to another Factors affecting this are (*a*) atmospheric conditions when maturing (in the case of pollens) (*b*) storage conditions—which with uncontrolled moisture can cause loss of antigenicity and (*c*) great variations in nutritional values of media used as in the case of growing mold mats Also pollen of different species varies greatly in potency and this cannot be taken into account when the same w/v standard is used for each pollen unless each pollen is tested at a different dilution

Second some mechanical sterilization procedures remove more antigenic material from an extract than do others One filtration through an asbestos Seitz filter pad is known

to remove some activity and if a second filtration is necessary more will be removed but no account can be taken of this in the w/v method of standardization

Third there is some question as to whether a 1 100 extract means 1 Gm dry antigen extracted in 100 ml of extracting fluid or 1 Gm dry antigen extracted successively in extracting fluid concentrated and made up to a final volume of 100 ml The matter would obviously yield a more active and concentrated extract

Unfortunately no authority has thus far defined this unit so that wide variations in potency of one 1 100 dilution of extract as compared to another is bound to exist because of the above mentioned variables

2 There is a good correlation between clinical reactivity and the nitrogen standards of allergenic extracts The activity seems to reside in the nitrogen fractions There may be active polysacchyride fractions but these may even be linked onto polypeptides or other nitrogen bearing units and until some better method of evaluating activity of the final extract is suggested the total nitrogen unit or protein nitrogen unit should be recognized as having many advantages over any w/v method of standardization

In standardizing an extract by the use of a total nitrogen unit or protein nitrogen unit the variables mentioned above are all taken into account because it is the amount of nitrogen in the final extract which is measured The nitrogen standard takes into account all of the variables such as the varying amount of activity in the original antigenic mass all dilutions concentrations extraction factors and loss of activity caused by filtrations

The total nitrogen or protein nitrogen is determined on the final extract after negative sterility tests are confirmed A macro or micro Kjeldahl nitrogen determination is performed in duplicate For the protein nitrogen unit (PNU) the method of Stull & Cooke [8, 9] should be carefully followed for phosphotungstic acid precipitable nitrogen since variations can cause wide differences in the amount precipitated A total nitrogen is then determined on the washed phosphotungstic acid precipitate giving the protein nitrogen which is then converted into the protein nitrogen unit The following table gives the conversion of mg of nitrogen into the unit system and is followed by a summary of the approximate equivalents of the various units

STANDARDS OF EXTRACTS

NOON UNIT

Based on original pollen weight to volume of extracting fluid (w/v)

1 noon unit = 1/1 000 000 Gm or 0 001 mg pollen (also called a pollen unit)

PROTEIN NITROGEN UNIT (PNU)

Based on protein nitrogen content of the extract

1 protein nitrogen unit = 0 00001 mg protein nitrogen per ml (also called a Cooke unit)

TOTAL NITROGEN UNIT

Based on total nitrogen content of the extract

1 total nitrogen unit = 0 00001 mg total nitrogen per ml (also called a pollen unit)

APPROXIMATE EQUIVALENCE OF VARIOUS UNITS

1 Protein nitrogen unit (Cooke) = 2 noon units = 1 500 000 w/v dilution = 2.6 total nitrogen units

In treatment with inhalant extracts strengths of 10 100 500 2 000 5 000 10 000 and 20 000 PNU per ml are useful

For intracutaneous testing (only after a complete history) the inhalants are first tested at 100 PNU strength Where no marked reaction has occurred the inhalants at *1 000 PNU* are tested at another visit Foods are generally tested at a 3 500 PNU strength however there are several important exceptions to this Fish egg and nuts are tested at only 100 PNU mustard at 50 PNU and milk at 1 000 PNU These foods are very potent antigens and generally if an individual is sensitive to one of this class he is exquisitely sensitive If he will react at all by skin test it has been found by experience that he will react to the aforementioned concentrations of extracts

The Routine Testing Series for intracutaneous testing as used at the Allergy Clinic of The University Hospital (New York University–Bellevue Medical Center) in New York City is as follows

TESTING SERIES

(expressed in PNU per ml)

POLLENS (Tested in 10 100 and 500 units)

Ash	Hickory	Timothy and orchard
Beech	Oak	Plantain
Birch	Poplar	Ragweed
	Series 1—Weak Inhalants	
Timothy and orchard 100	Cottonseed 100	Kapok 100
Plantain 100	Tobacco 100	Flaxseed 100
Ragweed 100	Dog epithelia 100	*Alternaria* 100
Dust concentrate	*Cat epithelia 100*	*Aspergillus* 100
Rabbit epithelia 100	Horse epithelia 100	*Penicillium* 100
Feathers 100	Horse serum 1–100	*Hormodendrum* 100
Orris 100	Pyrethrum 100	

Series —Strong Inhalants

Timothy and orchard 500	Cottonseed 1 000	Kapok 1 000
Plantain 500	Tobacco 1 000	Goat epithelia 1 000
Ragweed 500	Dog epithelia 1 000	*Alternaria* 1 000
Dust concentrate	Horse epithelia 1 000	*Aspergillus* 1 000
Rabbit epithelia 1 000	Cat epithelia 1 000	*Penicillium* 1 000
Feathers 1 000	Horse serum 1-10	*Hormodendrum* 1 000
Orris 1 000	Pyrethrum 1 000	

Series 3—Foods

Milk 1,000	Chicken 3,500	Tea 3,500
Egg 100	Pork 3,500	Coffee 3 500
Wheat 3,500	Lamb 3,500	Chocolate 3 500
Rice 3 5000	Beef 3 500	Mustard 50
Rye 3,500	Codfish 100	Coconut 100
Oats 3,500	Halibut 100	Peanut 100

Series 4—Fruits and Vegetables

Orange 3,500	Banana 3 00	Cucumber 3 500
Grapefruit 3,500	Onion 3,500	Lima bean 3 500
Peach 3,500	White potato 3,500	Pea 3,500
Prune 3,500	Cabbage 3,500	Tomato 3,500
Apple 3,500	Corn 3,500	Celery 3,00
Strawberry 3 500	Spinach 3,500	Cantaloupe 3 500

II THE PREPARATION OF SPECIAL ANTIGENIC EXTRACTS IN MORE DETAIL

A Pollens Pollens are generally defatted with ether and then extracted in Coca s solution In general 5 Gm of pollen are extracted in 100 ml of Coca s solution However some pollens notably plantain and most tree pollens contain less active material so that an 8 per cent extraction of these materials is more desirable for a more potent extract It is advantageous to make the first aqueous extraction with three fourths of the total volume of extracting fluid calculated for the total extraction After extraction and filtration the pollen is then re extracted with the remaining one fourth of the extracting fluid In this way more active material is extracted from the pollen It is also important to note that the pollen grains themselves are very acid and while a 5 per cent pollen extraction will reduce the initial pH of 8.2 of Coca s solution to 7 or 7 2 an 8 or 10 per cent pollen extraction will reduce the Coca s solution to a pH of approximately 6 In order to maintain a neutral pH the concentration of bicarbonate in Coca s solution should be proportionately increased when a more concentrated pollen extraction is made Pollen extracts are not dialyzed or concentrated and are then handled in the routine manner under General Procedures

B *Epithelial substances and other inhalants* Dog cat rabbit goat and sheep epithelial extracts are obtained by taking the whole skin and hair of the above mentioned animals air drying them and then either cutting them in very fine pieces or pulverizing them in a ball mill and then extracting as under General Procedures

C *Molds* Pure cultures of the individual molds are kept in stock on Sabaroud Agar slants and are subcultured every four to six weeks in order to maintain the colony After one week s growth at room temperature they are stored in the ice box All molds for production of the mold mat used for making the extract should be grown on synthetic media in order to avoid nonspecific reactions caused by foreign protein such as peptones in the media or by the irritation of agar All inhalant molds grew readily on the synthetic media described by Center[10] when we modified it to contain 15 per cent maltose and 15 per cent dextrose These two sugars were found to give better mold growth than 30 per cent sucrose as was suggested in the original Center formula The mold mat after growing for several weeks is homogenized with Coca s solution in a Waring Blender and at the same time is killed by adding 0 5 per cent tricresol to the total volume of the final mat and extracting fluid The rest of the extraction is carried out as under General Procedures

D *Fruits and vegetables* These foods are ground in a meat grinder or mixed with a small amount of extracting fluid and minced in an electric blender Most fruits and vegetables are very acid and are neutralized with 1 1 NaOH solution before extraction Otherwise the weak buffer capacity of the extracting fluids is immediately overrun and dialysis would be unnecessarily prolonged for equalization of the pH between extract and extracting fluid The rest of the extraction is carried out as described under General Procedures

In general the food tests have been unsatisfactory This may be because of the fact that the regular aqueous extracts of foods do not contain the antigenic material in sufficient testing concentration This is possible since there is 75 to 85 per cent water in most fruits and vegetables which are then diluted with extracting fluid and which unless concentrated many fold could not possibly contain sufficient protein or carbohydrate Then there is always the possibility that the individual is not sensitive to the food as eaten but to a degradation product such as a split proteose or pentose Because

of this there is a certain amount of data accumulating to suggest that acetone precipitated fruit and vegetable extracts are superior in activity and in nonspecific irritability to the aforementioned regular aqueous extracts If acetone is used for the precipitation all solutions should be maintained at 5C in order to retard denaturation during this procedure

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APPENDIX II

H Harold Gelfand

BOTANY AND ALLERGY

Many allergic disorders stem from plants and plant products Hay fever and asthma may result from the inhalation of various pollens of trees grasses and weeds as well as fungi Furthermore allergic contact eczema may be induced by poison ivy poison oak and poison sumac or infrequently by pollen For these reasons a brief review is presented of the botany involved in these phenomena Such a review can be most helpful in diagnosis treatment and prophylaxis

POLLEN AND POLLINOSIS

Durham [1] speaking of pollen and its identification says The allergist should know his pollens This should be broadened to include the general practitioner since he sees and treats most allergic disorders Furthermore he should incorporate as well a knowledge of the botany other than hay fever pollen and plants also etiologically implicated in allergy It is important that the physician familiarize himself with the common hay fever plants of the community in which he practices and the microscopic appearance of the specific pollen grains Regional calendars of the tree grass and weed seasons as prepared by Cooke [2] (Fig AII 1) Durham [1] Wodehouse [3] and others [4 7] supply additional information not available in this discussion

Before the presentation of the various pollens specifically involved in hay fever a brief description of the discovery of the role of pollen

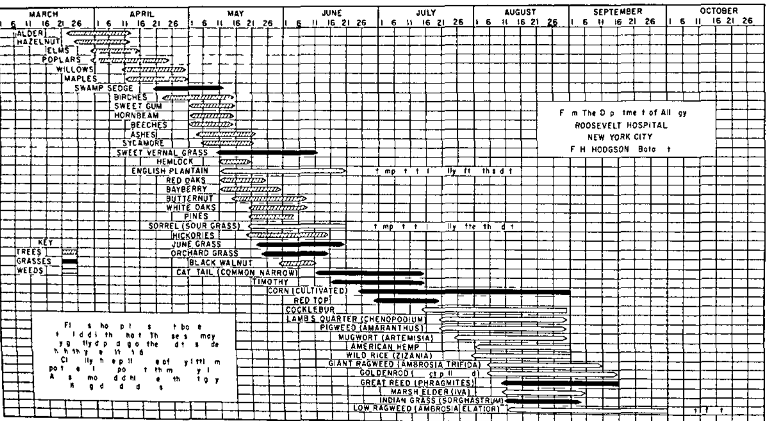


Fig XII 1 Chronology of air borne pollens (*From R A Cooke Allergy in Theory and Practice W B Saunders Company Philadelphia 1947 By permission of the author*)

is indicated Although Bostock[8] in 1828 coined the term *hay fever* gave it its first accurate description and associated it with grasses (hay) it remained for Charles Harrison Blackley[9, 10] in 1873 and 1880 to positively implicate pollen when he reported his experiments with both fresh and dried specimens of pollen from grasses and other plants He found them all active and suggested *pollen fever* and *pollen catarrh* as appropriate titles for the disorder He demonstrated the presence of pollen in the air by exposing glycerine coated slides for twenty four hour periods and found that 95 per cent of atmospheric pollen was derived from the grass family especially in the country as compared with city districts He pointed out the relationship between the amount of pollen in the atmosphere and the intensity of hay fever

Finally to bring this history up to the present one must include the work of Cooke[11, 15] and his group[16] whose study of hay fever clarified first the nature of the hay fever–causing substance in pollen and later the role of the blocking antibody as a factor in the production of clinical immunity in hay fever

THE PRODUCTION AND TRANSFERENCE OF POLLEN

Plants produce the pollen which is the exciting agent of seasonal hay fever However not all plants are involved in its causation The following postulates devised by Thommen *et al*[4] should be fulfilled in order to implicate a specific plant as a cause of periodic hay fever plant and pollen must be widely distributed pollen must be wind borne and it must be capable of exciting hay fever

Pollen consists of a cellular structure and a protective covering (Fig AII 2) The process of pollination is concerned with the transference of the pollen from the stamens (the male element) to the pistil (the female element)

The concentration and distribution of pollen grains depend on a number of climatic factors such as wind sunshine rainfall and humidity during the growing season of the plant

The transference of pollen grains during the life of the flower has a direct bearing on hay fever It is during the period of pollination that hay fever occurs Pollination may occur in any of the following ways (1) by insect (2) by wind (3) by water and (4) by self pollination Pollination by wind because of its importance will receive chief consideration here

Wind pollination is the outstanding type of pollen transference causing hay fever Plants which pollinate in this fashion are usually unattractive in appearance are comparatively small rarely have any

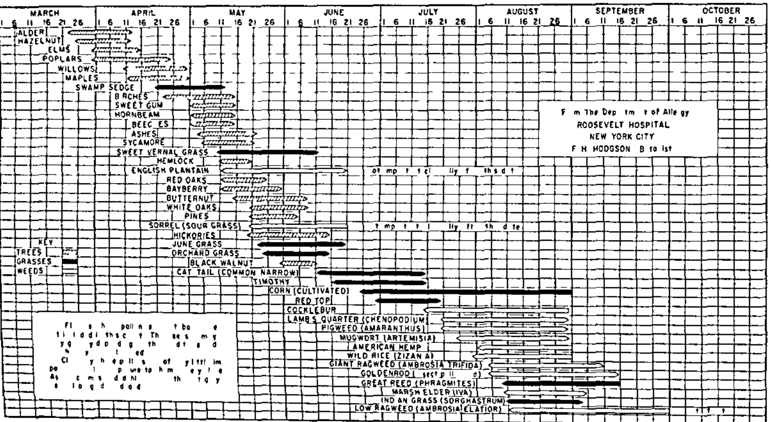


Fig XIII 1 Chronology of air borne pollens (*From R A Cooke Allergy in Theory and Practice W B Saunders Company Philadelphia 1947 By permission of the author*)

include the early or spring season (trees) the middle or summer season (grasses) and the late or fall season (weeds) These are fully discussed in Chapter 16 and the specific plants involved are described in Appendix III

A fourth and less important intermediary season has also been recognized and is presently described This season falls in between the grass and ragweed seasons and overlaps the latter It is of greatest importance west of the Mississippi and the following weeds in addition to ragweed may be involved

Various amaranths such as pig weed tumbleweed sage and artemisias	Hemp
	Wild rice
	Great reed
Chenopods (lamb s quarter)	Indian and marran grass
Ivas (marsh or burr elder)	Sedge
Cocklebur	Sugar beet
Russian thistle	Corn (cultivated)

These so called late fall weeds constitute an intermediate season in the Northeast Chobot and Dundy [4] studied a group of patients with hay fever symptoms occurring during the period between the grass and ragweed seasons namely from the last week of July until August 10 and found them etiologically related to the pollen of these late fall weeds

POLLEN IDENTIFICATION

For the proper identification of pollen a knowledge of its structure and the part it plays in the life of the flower is essential

Shape and Color Pollen grains usually are small ellipsoid or spherical and in different species vary in size from 3 to 210 microns in diameter In the majority of species they are yellow but exceptionally white or colorless examples may be found

Pollen Counts The two main methods for estimating the concentration of pollen in the atmosphere are the gravity and the volumetric methods In the former exposed coated slides trap the settling pollen which is then counted Proper precautions must be taken to insure accurate counts since obstructions impair the settling In the volumetric method samples of air are drawn into a special device containing coated slides over which the air passes and on which the pollen settles The method of counting is based on the number of pollen grains found in an area of about 1 sq cm in the twenty four hours of exposure

POLLEN FREE AREAS

No area is absolutely free of pollen There are however areas where the pollen may be sufficiently low in concentration to afford relief for the hay fever sufferer Such areas may be devoid of hay fever-producing plants because of competing flora or because of high altitude (over 6 000 ft) A sea voyage or other extensive trip on any large body of water will also minimize inhalation of pollen

Hay fever is primarily a disease of the temperate zones but it may also occur in mountainous tropical regions in which the vegetation is similar to that of the temperate climates

TABLE 52 POLLEN FREE AREAS

State	Area
California	Downtown San Francisco and Oakland
Canada	Province of Ontario wooded section Isle Royale and Belle Islands
Colorado	Leadville Georgetown Idaho Springs (all at altitude of 8 000 to 10 000 ft) Colorado Springs
Florida	Eastern coast
Maine	Coast especially eastern and northern parts Rangely Lakes
Mexico	Mexico City
Michigan	Mackinac Island Washington Island on Lake Michigan north shore of Lake Superior
Minnesota	Duluth Arrowhead region of northern Minnesota
New Hampshire	White Mountains
New Jersey	Atlantic City (for mild cases)
New York	Central Adirondack Mountains region north of St Lawrence River lower St Lawrence valley Lake Placid Montauk Point Fire Island
North Carolina	Great Smoky and Black Mountains
Oregon	Mount Hood area
Pennsylvania	Pocono Mountains
Tennessee	Roan Mountains
Texas	Gulf coast
Vermont	Green Mountains
Wisconsin	Eagle River

Mountainous areas in the United States where relief from hay fever may be afforded include the Adirondack Mountains in New York State the White Mountains in New Hampshire the Green Mountains in Vermont the Rocky Mountains in the West the Pocono Mountains in Pennsylvania the Great Smoky Mountains and Black Mountains in North Carolina and the Roan Mountains in Tennessee A number of lake regions including the Rangely

Lakes in Maine and Lake Placid in New York State will also be found relatively free of pollen

A list of areas in the United States and Canada including altitudes in many cases which would be beneficial to hay fever sufferers was compiled by Scheppegrell

Table 52 lists pollen free areas based on the report of the Society for the Study of Asthma and Hay Fever [6] and that of Taub [7]

POISON IVY POISON OAK AND POISON SUMAC (RHUS DERMATITIS)

These plants are weeds and are the specific excitants of a form of allergic inducible contact dermatitis occurring in individuals sensitized by previous contact [8-3] The reader is referred to Chap 33 for detailed discussion of poison ivy the most common form of this type of dermatitis

The weeds responsible for *Rhus* dermatitis are *Rhus toxicodendron radicans* which causes poison ivy and poison oak dermatitis and *Rhus toxicodendron vernix* which causes poison sumac dermatitis These weeds have a common excitant It is a polyhydric phenol highly soluble in alcohol ether and acetone It is contained in the root stem leaf flower and pollen of these plants In Appendix III a description is given to facilitate identification of these plants in order to help the sensitive individual to avoid contact

FUNGI (MOLDS RUSTS AND SMUTS)

The first report incriminating a fungus in allergic disease was that of Ancona [33] in 1922 Others who have contributed to a better understanding of these allergens include Van Leeuwen [34] Cadham [35] Hopkins *et al* [36] and Harris [3, 38]

There are 80 000 species of fungi characterized as undifferentiated plants devoid of chlorophyll which grow and develop on organic material synthesized by other organisms They are therefore either parasitic or saprophytic on animal or plant life Characteristically only fungi saprophytic on plant life cause allergic disease in man

The fungi subdivided in the order of their importance in allergy include molds rusts and smuts

Molds Molds are widely and abundantly distributed They may be locally confined or because of their small size disseminated into the atmosphere and blown many miles from their origin Atmospheric molds like pollen have diurnal seasonal and annual fluctuations Studies of the distribution of atmospheric molds indicate that

(1) There is a great abundance of these in the South with less seasonal variation than found in the North (2) *Alternaria* and *Hormodendrum* are the most commonly encountered and (3) *Penicillium* and *Aspergillus* although widely distributed geographically contribute little to atmospheric contamination

The mycelium which is a collection of branched cells is the most important part of the mold It is the vegetative or growing portion of the cell structure It secretes enzymes and acids which help to digest the material on which the mycelium grows

Fungi require for growth humidity exceeding 70 per cent Mold spores will germinate and mycelial fragments will therefore develop in moist areas such as damp basements and house foundations where there is plant and animal matter and dim light Molds also flourish in dust and overstuffed furniture

Molds produce spores in large quantities either of one kind only or of several different kinds They vary as to methods of reproduction which may be either sexual or asexual or a combination of both Molds are identified and classified on the basis of the characteristic spores they produce either by microscopic examination of spores trapped on exposed coated slides or by cultures developing on petri dishes that have been exposed to the air The plate or culture method in which characteristic colonies appear is more reliable than the slide method in which only the spores are used for identification Wherever possible cultures should be used to supplement and check the spores seen on the slide since only a limited number of molds whose spores possess a characteristic appearance and suitable size can be identified by this method

The following are the important molds encountered in allergic practice *Alternaria Hormodendrum Aspergillus*, and *Penicillium* Additional molds which may be responsible for allergic symptoms include *Mucor Monilia Saccharomyces* (yeasts) *Pullularia, Torula Rhizopus* and *Trichoderma* Occasionally one encounters *Chaetomium Macrosporium Cephalothecium Actinomyces Oospora Verticillium Botrytis Spicaria Mycogone*, and *Nigrospora*[39] (see Chap 43)

Although there has been some disagreement on the interpretation and value of skin testing with antigens extracted from molds it is now generally agreed that positive reactions are significant in the Northeast[40-47] if substantiated by the following [48]

1 An increase of symptoms during the summer (July 10 to August 15) between the grass and ragweed seasons (see Fig 43 2)

2 Continuing of symptoms after ragweed pollination ceases

3 Absence of symptoms in winter

4 Aggravation of symptoms by hot humid weather and musty damp rooms basements barns and hay lofts

Zink[49] who observed 705 patients allergic to molds noted 56 per cent with allergic rhinitis 34 per cent with asthma primarily and the balance showing miscellaneous reactions in the skin eyes and sinuses

Rusts and Smuts Both these groups of fungi are parasites of plants most of which are grain bearing (wheat barley clover oats and sunflower) Like the molds they are spore producers but are not so readily identifiable nor are they culturable on petri dishes Rusts have a rusty complexion when growing on plants while smuts produce black spore masses and impart a dirty appearance to their host

The allergenicity of grain dusts and smuts was studied by Harris[3 35] clinically and immunologically He found them potent allergens and indicated that antigenically the grain dusts (including *rusts and smuts) are not related to molds The smuts show some* common antigenicity but are not completely identical

Waldbott and Ascher[50] reported cases of rust and smut allergy in which the symptoms were caused specifically by these allergens alone Wittich and Stakman[71] also reported cases of respiratory allergy due to these fungi Their patients showed positive skin reactions and benefited from the desensitization therapy instituted with extracts of smut spores In view of this rust and smut allergy assumes importance in the grain growing areas where these air borne allergenic agents may cause respiratory symptoms

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APPENDIX III

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THE HAY FEVER–PRODUCING PLANTS, POISON IVY, OAK, AND SUMAC

Trees

Many trees causing hay fever bear flowers on an elongated common axis known as a tassel or catkin The male flowers on a catkin have stamens in which the pollen grains are produced and shed in abun dance when the flowers open

The catkin bearing trees include the oaks hickories walnuts poplars beeches and birches Other trees considered here are the elm and the ash which do not bear flowers in catkins (See Fig AII 1 for additional trees causing hay fever) In Texas and Bermuda cedar may also cause hay fever

Of the pollinating plants the trees are least important in causing hay fever

The Oaks There are a few hundred known species of oak about twenty of them prominent in the Eastern States These include the white oak (*Quercus alba*) black oak (*Quercus velutina* Fig AIII 1) red oak (*Quercus rubra*) and scarlet oak (*Quercus coccinea*)

The pollen bearing flowers of the oak hang like tassels in catkins about 2 or 3 in in length Pollen is shed chiefly in May The acorn the fruit of the tree is characteristic of all oaks each species having its distinctive type

The Hickories About ten species of hickory are native to eastern North America (Fig AIII 2) The distribution ranges from Quebec to

southern Ontario and Minnesota and south to Florida Kansas and Texas It is a common tree in New York State

The Poplars Among the various species in the vicinity of New York are the white poplar (*Populus alba*) the aspen (*Populus tremuloides*) and the large toothed aspen (*Populus grandidentata*)

Early swamp poplar (*Populus heterophylla*) by virtue of its heavy pollen production is our most important hay fever poplar



Fig AIII 1 Black oak (*Quercus velutina*) Its bark is furrowed and dark gray Distribution is from Maine to Florida and westward to Minnesota Kansas and eastern Texas

The Birches The birch tree is found chiefly in eastern United States There are seven species found in New York State and vicinity The gray birch (*Betula populifolia*) the yellow birch (*Betula lutea*) the river birch (*Betula nagra*) and the black birch (*Betula lenta*) are the most common varieties The birch is an outstanding pollen producer



Fig AIII 2 Shagbark hickory (*Hicoria ovata*) This tree grows [illegible] of 100 ft Its bark presents a shaggy appearance the leaves are [illegible] pinnate usually with five leaflets and its flowers appear as [illegible] kins (*Photograph copyright by Bergman Associates By perm* [illegible])

Grasses

The troublesome grasses in regard to hay fever [illegible] plantain and sorrel which usher in the season about [illegible] May followed by orchard timothy red top June [illegible] grasses These grasses shed enormous amounts of [illegible]

June and cause considerable hay fever and asthma In the south the commonly implicated grasses are Bermuda and Johnson grasses

The grasses encompass not only the meadow and lawn varieties but also hundreds of wild and cultivated species including the cereal grains in the majority of which the pollens are air borne and thus potentially allergenic

Fig XIII 3 English plantain (*Plantago lanceolata*) Sometimes called rib grass It is distributed throughout North America

Among over 4 000 different species of grasses throughout the entire world approximately 300 are to be found within and around New York City In the United States grasses are superseded in importance as a cause of hay fever only by the ragweed and composite families

Although the grasses may differ in many respects their pollens resemble one another closely and differ sharply from the pollens of

other plant families The grasses have common antigens so that it is not necessary to treat with mixtures of all the grass pollens as with tree pollens

There are many grasses whose pollen causes hay fever only the important ones receive consideration here

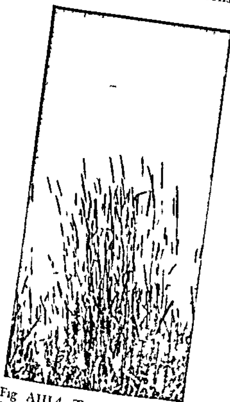




Fig AIII-4 Timothy grass (*Phleum pratense*) Grows to a height of 1 to 3 ft and is erect and unbranched The flowers occur in a cylindrical spike (*Photograph copyright by Bergman Associates By permission*)

English Plantain (*Plantago lanceolata* Fig AIII 3) This is sometimes called rib grass because of its heavily veined leaves which are thick narrow hairy on both sides oblong and tapered arising from a tall stalk bearing tiny white flowers in a cylindrical head The plant reaches a height of about 2 ft

Imported from Europe English plantain has become a very troublesome plant in eastern United States It is the only member of the plantain family which is of any importance in hay fever Its pro

duction of pollen is only moderate It is an aggressive weed it injures lawns and may be found in countless numbers in every lot and in waste places

Timothy Grass (*Phleum pratense* Fig AIII 4) This grass imported from Europe and Asia is widely distributed throughout nearly all of North America because it has been extensively cultivated for hay It pollinates heavily from the last week of June to the latter part of July and its pollen is of great importance in hay fever While it



Fig AIII 5 Orchard grass (*Dactylis glomerata*) Grows to a height of 2 to 4 ft and is cultivated for hay Distributed from Manitoba to South Carolina and west to Kansas (*Photograph copyright by Bergman Associates By permission*)

is grown in great abundance in fields and meadows in agricultural districts large quantities may also be seen on waysides and in vacant lots in New York City

Timothy grass grows from 1 to 3 ft tall, erect and unbranched The flowers occur in a cylindrical spike at the top of the stem about 2 to 5 in long and about ¼ in wide Because of its cylindrical spikes it is one of the easiest grasses to recognize

Orchard Grass (*Dactylis glomerata*, Fig AIII 5) Orchard grass came originally from Europe and Asia It has been cultivated for

fodder in many parts of the United States and pollinates mostly in June

The stems are from 2 to 4 ft tall They grow in tufts and are erect unbranched and smooth The flowering heads grow on one side of the flowering branches in dense clusters at the tips The flowering



Fig AIII 6 Redtop grass (*Agrostis alba*) Grows 1 to 2½ ft tall The flower is purplish red the plant is extensively cultivated for fodder

portion of the plant is from 3 to 5 in in length and pale green in color It may be found in fields and vacant lots and on neglected roadsides through the entire country

Red Top (*Argostis alba* Fig AIII 6) This grass came from Europe originally but is now found throughout North America It is cultivated for cattle fodder

The plant s flowering portion has a purplish color which helps to distinguish it from other grasses It grows from 1 to 2½ ft tall is smooth and has a shiny open flowering head from 2 to 9 in in length Pollination occurs at the same time as pollination of timothy grass



Fig AIII 7 High ragweed (*Ambrosia trifida*) It has opposite sandpapery leaves which have three to five pointed lobes with saw toothed edges May reach a height of 10 ft

Weeds

High Ragweed (*Ambrosia trifida* Fig AIII 7) This is one of the most troublesome plants from the standpoint of producing hay fever It flowers from mid August until late in September producing countless numbers of pollen grains from its inconspicuous flowers It has opposite sandpapery leaves which usually have three sometimes five pointed lobes with saw toothed edges Some of the upper leaves however may be round and not lobed The male flowers which produce the pollen are usually borne in a spike at the top of the plant and the ends of the branches

This weed is most abundant in the Mississippi valley from Texas

to Minnesota and in the Dakotas It also occurs in the East In New York City it is abundant in empty lots where it reaches a height of over 10 ft It pollinates constantly from the latter part of August through September



Fig XIII 8 Low ragweed (*Ambrosia artemisifolia*) The spines are closer smaller and less pointed than in high ragweed The height ranges from 1 to 5 ft

Low Ragweed (*Ambrosia artemisifolia* Fig XIII 8) The flowers and pollen of this plant closely resemble those of the high ragweed The leaves however are fernlike that is finely divided The plant grows from 1 to 5 ft high

Low ragweed came originally from Europe and is now very common in eastern North America the Rockies the Pacific Northwest Mexico the West Indies and South America



Fig AIII 9 Poison ivy and poison oak (*Rhus toxicodendron radicans*) These are usually seen as climbing vines but also appear as erect bushes or trailing shrubs The leaves have long stalks bearing three leaflets The middle leaflet has a short petiole the others are sessile When climbing a tree they can reach a height of 30 to 40 ft (*Photograph copyright by Bergman Associates By permission*)

POISON IVY POISON OAK AND POISON SUMAC

Rhus toxicodendron radicans (poison ivy and poison oak Fig AIII 9) can be seen occasionally as an erect bush growing to a height of 4 ft at times as a trailing shrub but most often as a climbing vine The leaves are characteristic and can be easily recognized by the fact that they have long stalks bearing three leaflets the middle leaflet having a short petiole the others sessile The upper surfaces are shiny and at certain stages are red Poison ivy when climbing a tree will sometimes reach a height of 30 to 40 ft and a stem diameter of 2 in or more

Rhus toxicodendron vernix (poison sumac Fig AIII 10) grows in swamps and usually attains a height about three times that of poison ivy or up to 10 ft or more it is characterized by having more slender stems than ivy Poison sumac is not vinelike but an erect shrub or small tree Its mature height is apt to be about 15 ft in the eastern United States



Fig AIII 10 Poison sumac (*Rhus toxicondendron vernix*) Grows in swamps to a height of about 10 ft as an erect shrub The stems are slender not vinelike (*Photograph copyright by Bergman Associates By permission*)

APPENDIX IV

ORGANIZATIONS AND INSTITUTIONS ACTIVE IN THE FIELD OF ALLERGY

I ORGANIZATIONS FOR THE ADVANCEMENT OF KNOWLEDGE IN ALLERGIC DISEASE

There are in the United States four organizations of nation wide scope for the advancement of knowledge of allergic disease These are the American Academy of Allergy the American College of Allergists the Allergy Foundation of America and the National Institute of Allergy and Infectious Diseases

The American Academy of Allergy

The American Academy of Allergy was established in 1943 by merger of the Association for the Study of Asthma and Allied Conditions founded in New York City in 1923 and the American Association for the Study of Allergy founded in San Francisco in 1924

Before the merger of the two societies they had met together and jointly initiated the publication of the *Journal of Allergy* in 1929 and had also established a Joint Committee on Standards to consider the status and quality of allergy clinics throughout the United States

The object of the Academy is the advancement of the knowledge and practice of allergy by discussion at meetings by fostering the education of students and the public by encouraging union and cooperation among those engaged in this field and by promoting and stimulating research and study in allergy

The membership of the Academy consists of members fellows affiliate fellows emeritus fellows honorary fellows and inactive mem

bers with qualifications according to the type of membership There are now about one thousand members in all categories The *Journal of Allergy* is the official publication of the Academy

In addition to the usual standing committees of any medical or ganization the Academy has a committee on Audio Visual Education an Editorial Board a Committee on Graduate and Undergraduate Education an International Committee and the Research Council The Council in turn is subdivided into committees on Aero allergens Weather Contactants Drugs and Food Allergy

An annual meeting is held preceded by a three day session of postgraduate discussion and instruction Scientific and commercial exhibits also feature these meetings

The address of the executive office of the Academy is 756 North Milwaukee Street Milwaukee 2 Wisconsin

The American College of Allergists Inc

The American College of Allergists Inc founded in 1942 like the American Academy of Allergy is an organization of physicians

The object and purposes of the American College of Allergists are

1 To establish an organization of qualified physicians and scientists who will meet for the purpose of promoting and advancing the study of laboratory and clinical knowledge of allergy

2 To advance and maintain the highest possible standards of the practice of the specialty of allergy

3 To perpetuate the best traditions of medicine and medical ethics

4 To establish standards for qualification and procedures for the certification of physicians in the specialty of allergy

5 To maintain the dignity of the specialty in its relation to the public welfare

6 To promote friendly intercourse and relationship between and among those in the practice of allergy

In addition to the usual standing committees of any medical association the College has a committee on New and Untried Therapeutic Preparations Aero biology Psychosomatic Aspects of Allergic Disease and Public Education

The membership of the College consists of active fellows honorary fellows associate fellows and corresponding fellows with qualifications according to the type of membership

The official publication of the College is the *Annals of Allergy* issued bimonthly

An annual meeting is held preceded by a three day session of post

graduate instruction and discussion over a three day period with a large number of scientific and commercial exhibits

The address of the executive office of the College is 401 La Salle Medical Building Minneapolis 2 Minnesota

The Allergy Foundation of America

The Allergy Foundation of America was established under the name of The American Foundation for Allergic Diseases in 1953 by the American Academy of Allergy and the American College of Allergists

The object of the Foundation is to improve medical treatment of allergic disease by aiding research by improved and expanded training of basic scientists and physicians and providing a better understanding of allergic disease on the part of the public In addition the Foundation hopes to provide a national health program for the allergic patients to be administered under the auspices and supervision of organizations working at the local community level

The organization consists of a Board of Trustees comprised by laymen educators and physicians the Scientific and Educational Council the Medical Director the Executive Director and Regional Councils of Allergists

The Board of Trustees makes the policies which govern the activities of the Foundation and assumes responsibility for raising and distributing the funds necessary for these activities

The Scientific and Educational Council is charged with the responsibility of developing the research and medical education program and making recommendations as indicated to the Board of Trustees It also supervises grants for research

The Medical Director administers the research and professional program supervises the medical content of all publications assumes staff responsibility for all activities of the Scientific and Educational Council and the disposition of the many medical inquiries received by the Foundation

The Executive Director is responsible to the President of the Foundation and through him to the Board of Trustees for over all direction coordination and implementation of policies and decisions of the Board

The Regional Councils of Allergists are organized to bring all allergists into closer contact with the work of the Foundation and secure their help in carrying out the broad national objectives for which the Foundation stands

The Foundation is located at 801 Second Avenue New York City 17 New York

The National Institute of Allergy and Infectious Diseases

The National Institute of Allergy and Infectious Diseases formerly known as the National Microbiological Institute one of the seven National Institutes of Health research arm of the U S Public Health Service was established December 1955

The objective of the Institute is to conduct and support research on human diseases caused by microorganisms and by allergic reactions and to investigate related fundamental problems

The Institute s direct operations are carried out through five principal divisions the Laboratory of Immunology to expand research in the field of Allergy Immunology the Laboratory of Infectious Diseases the Laboratory of Tropical Diseases the Rocky Mountain Laboratory and the Laboratory of Clinical Investigation The divisions are all located at Bethesda Maryland with the exception of the Rocky Mountain Laboratory the Institute s center for the study of animal diseases transmissible to man which is in Hamilton Montana

In addition to its program of direct research the Institute administers an extensive grants program to foster research in the nation s universities and medical schools This program which was greatly enlarged in 1956 includes the support of fellowships research projects and a recently initiated program of training grants

It is hoped that the expanded research program now being completed by the Institute will accelerate progress against certain disease areas which have long resisted attack The allergic diseases and virus diseases are notable examples of such fields Both are in need of much long term basic research

II HOSPITALS SCHOOLS AND HOMES FOR THE TREATMENT OF ASTHMATIC PATIENTS

There are a number of nationally known institutions (homes schools and hospitals) providing treatment for the severely asthmatic patient Most of these are institutions catering exclusively to children with the exception of the National Jewish Hospital of Denver which also has a program for adult asthmatic patients

The National Jewish Hospital

The National Jewish Hospital at Denver is a 325 bed nonsectarian free-care medical center for treatment research education and rehabilitation in diseases of the chest including asthma

The asthma program has been developed around the concept of

long term hospitalization and the ready availability of the complex facilities and services of a modern hospital It is under the direction and supervision of a qualified internist The services provided include

1 Allergy diagnosis and therapy

2 Psychiatric psychological and social case work services

3 Pulmonary and cardiac physiological evaluation including cardiac catheterization ventilatory functions pulmonary circulatory studies and angiocardiography when indicated

4 Thoracic and cardiac surgical services are available if indicated

5 Rehabilitation services are available including vocational counselling and training formal academic education physical therapy and occupational therapy The program aims to return the patient to his home and community fully able to function effectively

Extensive research activities both basic and clinical are carried on in a well equipped and staffed department of research Special areas of interest are in the fields of immunology and hypersensitivity cardio pulmonary physiology and chemotherapy

The asthma program provides for all age groups The pediatric service is housed separately from the adult service

The Hospital is located at 3800 East Colfax Avenue Denver 6 Colorado

The Betty Bacharach Home for Asthmatic Children

The Betty Bacharach Home in Longport New Jersey has recently established an Asthmatic Unit for the residential treatment of children with uncontrolled asthma The Home is a pediatric institution of national reputation It was established 34 years ago and over three thousand children have been treated as in patients Forty beds are presently available for the care of children with intractable asthma The Asthmatic Unit is a separate entity and all of its facilities are used exclusively by the asthmatic children

The Betty Bacharach Home is located in Longport the southern most tip of Absecon Island just south of Atlantic City New Jersey Although climate and environmental factors play little role in the results achieved in the treatment of intractable asthma there is an advantage in the fact that Absecon Island is relatively pollen free

The primary objective of treatment is of course the arrest or cure of the asthma Every effort is made to do this in as short a time as possible The pediatric allergist and psychiatrist in conjunction with the other members of the professional staff plan all treatment with these objectives in mind The unit is associated with the pediatric medical and psychiatric departments of Jefferson Medical College in Philadelphia and consultations are readily available

The facilities are particularly well adapted to this program The children are paired off into groups of three or four living in separate cubicles on a large ward Approximately 20 children live in one ward area The children are served in a spacious dining room The house mother eats with the children guiding their conversation to some extent and carrying on the general duties of a mother at home A large auditorium is used as a meeting room and gymnasium There is a library and a play room set aside exclusively for the use of the asthmatic children Outside athletic recreational facilities are available in a large spacious yard and a beach is within 500 feet of the Home Schooling for the children is provided in the Institution Conventional school rooms have been constructed and a maximum of 15 children are assigned to each teacher All children are tested by our psychologist and placed in a school grade commensurate with their ability

The treatment of the asthmatic child is all inclusive It is based upon the premise that practically all asthma is organic in origin The importance of the psychosomatic element in these intractable asthmatics is recognized Treatment is directed at both the organic and psychic elements

There is control of all possible environmental allergenic factors On admission following a complete history and physical examination the child is evaluated from an allergic point of view The children are hyposensitized if the history and skin testing suggest the necessity for this type of treatment Acute attacks of asthma are treated conventionally with bronchodilators adrenocortical steroids when necessary and other methods directed at achieving the most rapid relief of the attack

The asthmatic child is evaluated psychiatrically on admission to the institution The program of psychiatric therapy is a total psychotherapeutic effort with emphasis on a well rounded routine exercise outdoor play and group and individual therapy Pharmacological agents are used when indicated The parents are referred to a psychiatrist or a psychiatric clinic in their immediate vicinity They are required to be evaluated psychiatrically and if necessary continue with treatment so as to prepare for the return of the child to its own environment In addition the parents are requested to attend the session of group psychotherapy given at the Betty Bacharach Home once monthly

A house mother is assigned to each group of 20 children There is always a nurse on duty with the house mother These two are responsible for the day to day routine of the child

Visiting is permitted once a month Visiting is limited to an as-

signed week end The child may be taken from the Home during this visiting session

All children admitted to the unit are supported by the Betty Bacharach Home If the parents are in a position to afford partial or complete medical care of this type they are requested to contribute to the support of their child within their individual means Children ages five to fifteen years with intractable asthma are eligible for admission to the Asthmatic Unit Application blanks can be obtained by writing directly to the Betty Bacharach Home Longport New Jersey

The Sahuaro School

The National Foundation for Asthmatic Children at Tucson was incorporated in 1949 as a nonprofit nonsectarian philanthropic educational and research organization under the laws of the State of Arizona

In 1951 the National Asthmatic Foundation acquired one of the best private school plants for the implementation of its work with asthmatic needy children The Foundation began operation as a Foundation and with the basic policies now in effect September 1 1954 Since that time the Foundation has cared for 170 asthmatic children from all areas of the United States and from two foreign countries

The Foundation limits itself to children between the ages of six and twelve because of the desire to deal with reversible asthmatic changes our experience substantiates the conclusion that this age bracket is one of great response and recovery

Medical dental psychological physical therapy and other health care is provided for scholarship children in need of the type of care provided

The Foundation maintains and operates Sahuaro School located on the Foundation grounds The School is staffed by teachers familiar with the asthmatic child It provides complete schooling from the first through the eighth grade

Children between six and twelve years when medically eligible are accepted from (1) families who cannot pay anything toward the child s care and (2) those whose parents can contribute a portion of the cost On application in addition to the medical report received from the family doctor each child must be screened by a Fellow of the American Academy of Allergy Following the medical reports a complete social history from an accepted social agency must be forwarded to complete the application

The Foundation in addition to a complete school program pro

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The Foundation in addition to a complete school program pro

vides modern comfortable dormitories a well equipped infirmary with 24 hour nursing care and a diversified recreational program geared to the asthmatic child s need and ability

The Foundation is at present planning an expansion program it has disposed of the present site and has purchased 85 acres on which will be erected an entirely new plant to accommodate 120 children (present capacity 62 children) The new plant will be constructed on the cottage plan limiting capacity to ten children to each cottage Laboratory and other necessary space will be pro vided to start a program of research

The address is Sahuaro School P O Box 1551 Tucson Arizona

The Jewish National Home for Asthmatic Children and The Children s Asthma Research Institute and Hospital

The Jewish National Home for Asthmatic Children had its origin in 1907 as a home for the sheltering care of the well children of the tubercular poor In 1940 the National Home for Jewish Children initiated a program for the rehabilitation of the child with intractable asthma based upon the separation of the child from the parents the home environment and his removal to the institutional program at the Denver Home A number of changes in the development of the program along physical and psychological lines thereafter were imple mented with what appeared to be increasing measures of success in the control of the condition The facilities at the Home in Denver were expanded to permit the care of 150 children and to emphasize a nonsectarian policy and the name was changed in 1952 to The Jewish National Home for Asthmatic Children The present Medical and Research Director was appointed in July 1958 and was charged with the responsibility of developing an increased medical and research program for the analysis of the problems of intractable bronchial asthma of children

During 1957 the Jewish National Home for Asthmatic Children expanded its interest in the field of research and with the aid of a grant from the United States Public Health Service proceeded with the construction of an Institute devoted to research primarily in asthma but also in other related allergic diseases this to be known as the Children s Asthma Research Institute and Hospital This structure has been completed and put to use during the summer of 1959

The Jewish National Home for Asthmatic Children presently con sists of 13 brick structures situated on a 17½ acre tract of ground in the west end of the city of Denver in a residential community located at the foothills of the Rocky Mountains Seven of these structures provide cottage dormitory facilities for the resident patients and the

remainder comprise administrative buildings dining room power plant residential structure for attending physician or resident physicians temporary hospital and research areas and a building for the dental services rehabilitation services and group services including therapy

There are 150 children in residence at all times These children reside with houseparents who are carefully screened before selection and whose function as nearly as it is possible to do so is to create a warm parental environment and supervision for the children during their residence Children attend the Denver public schools the elementary grade school being located some four blocks distant from the Home and the Junior High School located directly across the street from the Home

The Medical and Research Director assumes all responsibilities for functions relating to the medical care and rehabilitation of the child This includes in addition to the basic medical needs and the special allergic management psychodiagnostic and psychotherapeutic services which represent a very important part of the medical program There is an especial interest in the emotional problems of the patients and their families because the intractable asthmatic child referred to the Jewish National Home for Asthmatic Children from all parts of the country by very competent physicians has already received all forms of allergic and other medical management with no significant benefit The Psychiatric Service consists of a staff psychiatrist and a consulting psychiatrist the latter available to us for policy making and special consultation functions

In summary the whole approach to the management of the asthmatic child at the Jewish National Home for Asthmatic Children is one which treats the child as an unique individual The principles of management of the total child are foremost and due consideration is given to allergic infectious environmental and psychogenic factors The address of the Jewish National Home for Asthmatic Children is 3147 West 19th Avenue Denver 4 Colorado

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